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(54) NOVEL PENICILLINS AND CEPHALOSPORINS AND PROCESS FOR PRODUCING THE SAME



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· •	(71) We, TOYAMA CHEMICAL CO. LTD., a corporation organised under the laws of Japan, of 1—18, Kayabacho, Nihonbashi, Chuo-ku, Tokyo, Japan, do hereby declare the invention for which we pray that a patent may be granted to us and	
	the method by which it is to be performed to be particularly described in and by the	•
. 5	following statement:— This invention relates to novel penicillins and cephalosporins and to a process for	5ٍ.
	The compounds of the present invention have various characteristics including a	پائسا د
	broad antibacterial spectrum against Gram-positive and Gram-negative bacteria, and	
10	effective antibacterial activity particularly against <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> and <i>Proteus</i> species. Furthermore, the compounds of the present invention possess high resistance to β -lactamase produced from bacteria, and effective antibacterial activity even against clinical isolates of bacteria which are significant at present from the clinical standpoint. Accordingly, the compounds of the present invention are	10
15	quite effective as therapeutic drugs for human and animal infectious diseases derived	15
,	from the above-mentioned pathogenic microorganisms. It has heretofore been known that 6-acylamino penicillanic acids and 7-acylamino-cephalosporanic acids having an amino group at the \(\alpha\)-position of the acyl group show strong antibacterial activity not only against Gram-positive bacteria but also against	
20	Gram-negative bacteria. However, there are the disadvantages that the known compounds described above show substantially no effective antibacterial activity against not only <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> and <i>Proteus</i> species, which have been known as causes for clinically serious infectious diseases but also resistant bacteria	20
25	which are frequently isolated at present from many clinical hospitals. And they tend to be hydrolyzed with β -lactamase produced from many drug-resistant bacteria. With an aim to obtain penicillins and cephalosporins having no disadvantages mentioned above, the present inventors conducted extensive studies to find that novel compounds of formula (I) which appears hereinafter, which are prepared by bonding the moiety,	25
	(x) _n	
30	$A - N \longrightarrow N - C - N - N$	30
	wherein A, X, Y, R ² , R ³ , n and m are as mentioned hereinafter, to the amino group in the acyl group of penicillins and cephalosporins, can sufficiently satisfy the above-mentioned aim and have extremely valuable therapeutic effects.	
35	It is an object of this invention to provide novel penicillins and cephalosporins containing a mono- or di-oxo- or thioxo-piperazino(thio)carbonylamino group in molecule.	35
	It is another object of this invention to provide novel penicillins and cephalosporins having a broad antibacterial spectrum.	
40	It is a further object of the invention to provide novel penicillins and cephalosporins having high resistance to β -lactamase produced from bacteria.	40
	It is a still further object of the invention to provide novel penicillins and cephalo- sporins having effective antibacterial activity against clinical isolates of bacteria. It is a still further object of the invention to provide a process for producing the	:
45	novel penicillins and cephalosporins. It is a still further object of the invention to provide a pharmaceutical composition containing the novel penicillins or cephalosporins as active ingredient. Other objects and advantages of this invention will become apparent from the fol-	45 ₹
	lowing description.	المنسريين .
50	The compounds of the present invention are penicillins and cephalosporins represented by the general formula (I),	50=
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$$A - N = \begin{bmatrix} (X)_n \\ X \\ X \end{bmatrix} = \begin{bmatrix} (X)_n \\ X \end{bmatrix} =$$

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wherein R represents an amino acid residue; R1 represents a hydrogen atom, an ester-forming group capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions, an ester-forming group capable of being easily removed by mamalium enzymic action, a silicon-, phosphorus- or tin-containing group which is capable of being easily removed by treatment with H2O or an alcohol, or a 5 conventional salt-forming cation, n represents 1 or 2; nX's, which may be the same or different, represent individually an oxygen or sulfur atom, and are linked in any combination at the 2-, 3- and 5- positions of the piperazine ring; m represents 4-n; each pair om R² and R³ is linked to the same carbon atom, and m pairs of R² and R³, which may be the same or different, represent individually a hydrogen atom, a halogen atom, a 10 carboxyl group or an unsubstituted or substituted alkyl, cycloalkyl, aryl, acyl, aralkyl, alkoxycarbonylalkyl, acyloxyalkyl, alkoxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, amino or carbamoyl group, any pair of R2 and R3 together with a comon carbon atom may form a cycloalkyl ring; A represents a hydrogen atom, a hydroxy group, a nitro group, a cyano group, or an unsubstituted or substituted alkyl, 15 alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, acyl, aralkyl, acyloxyalkyl, alkoxy, cycloalkyloxy, aryloxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, carbamoyl, thiocarbamoyl, acylcarbamoyl, acylthiocarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkylsulfonylthiocarbamoyl, arylsulfonylthiocarbamoyl, sulfamoyl, alkoxycarbonylthioalkyl, alkoxythiocarbonylthioalkyl, amino or heterocyclic group; Y 20 represents an oxygen or sulfur atom; and

where R' represents a hydrogen atom, a hydroxy group, a cyano group, an azido group, a quaternary ammonium group, or an unsubstituted or substituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, cycloalkyloxythiocarbonylthio, amidinothio or heterocyclylthio group.

alkyloxythiocarbonyithio, amidinatino of neterocyclythio group. In the above-mentioned general formula (I) R represents an amino acid residue. Examples of such amino acid residue include residues of amino acids derived from various aliphatic, araliphatic, aromatic, alicyclic and heterocyclic compounds, which amino acids may have the amino group at a position such as α -, β - or γ -position to the carboxyl group. Preferable as said R is an α -amino acid residue represented by the formula

wherein R³ is an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, or octyl; a cycloalkyl group such as cyclopentyl, cyclohexyl, or cyclohetyl; a cycloalkenyl group such as cyclopentenyl, or cyclohexenyl; a cycloalkadienyl group such as cyclopentadienyl, or cyclohexadienyl; an aryl group such as phenyl or naphthyl; an aralkyl group such as benzyl or phenetyl; an aryloxy group such as phenoxy or naphthoxy; an alkylthioalkyl group such as methylthiomethyl, ethylthiomethyl, methylthioethyl or ethylthioethyl; or a heterocyclic group such as furyl, thienyl, oxazolyl, hisoxazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, pyridyl, pyrazyl, pyrimidyl, pyridazyl, quinolyl, isoquinolyl, quinazolyl, indolyl, indazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-thiadiazolyl or 1,2,4-thiadiazolyl; each group represented by said R³ may be substituted by various groups, for example, halogen, hydroxy, nitro, alkyl, alkoxy, alkylthio, acyl, or alkylsulfonylamino; R⁶ represents a hydrogen atom; and R³ and R⁶ together with a common carbon atom may form a cycloalkyl ring such as cyclohexyl or cyclohexenyl; a cycloalkenyl ring such as cyclopentadienyl or cyclohexenyl; or a cycloalkadienyl ring such as cyclopentadienyl or cyclohexadienyl.

In the general formula (I), R1 is a hydrogen atom, a blocking group or a saltforming cation. The blocking group may be any of those which have heretofore been

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used in the field of penicillin or cephalosporin type compounds. Concretely, the blocking group includes (1) ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions e.g. arylsulfonylalkyl groups such as toluene-sulfonylethyl, substituted or unsubstituted aralkyl groups such as benzyl, 4-nitrobenzyl, diphenylmethyl, trityl and 3,5-di(tert.-butyl)-4-hydroxybenzyl; substituted or unsubstituted alkyl groups such as tert.-butyl, trichloroethyl, phenacyl groups; alkoxyalkyl groups such as methoxymethyl; and unsubstituted or alkyl-substituted cyclic aminoalkyl groups such as piperidinoethyl, 4-methylpiperidinoethyl, morpholinoethyl or pyrrolidinoethyl, (2) ester-forming groups capable of being easily removed owing to enzymes in a living body, e.g. acyloxyalkyl groups such as pivaloyloxymethyl; phthalide group; and indanyl group; (3) silicon-containing groups, phosphorus-containing groups and tin-containing groups which are capable of being easily removed by treating with H₂O or an alcohol, such as

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$$\{CH_3\}_3Si-$$
, C_2H_5O $P-$, or $\{C_4H_9\}_3Sn-$,

The examples of the blocking groups mentioned in above (1), (2) and (3) are merely 15 typical, and other examples are disclosed in U.S. Patents 3,499,909; 3,573,296 and 3,641,018 and DOS 2,301,014; 2,253,287 and 2,337,105 and may be used in this invention. The salt-forming cation includes conventional cations which have heretofore been known in the field of penicillin or cephalosporin type compounds, ad preferable are those capable of forming non-toxic salts. The salts include alkali metal salts such as 20 the sodium salt or the potassium salt; alkaline earth metal salts such as the calcium salt or the magnesium salt; ammonium salt; and salts with nitrogen-containing organic bases such as procaine, dibenzylamine, N-benzyl- β -phenethylamine, 1-ephenamine, or N,N-dibenzylethylenediamine. In addition to the above cations, there may be used cations capable of forming the salts with other nitrogen-containing organic bases, such 25 as trimethylamine, triethylamine, tributylamine, pyridine, dimethylaniline, N-methylpiper-idine, N-methylmorpholine, diethylamine, or dicyclohexylamine. Furthermore, the cation includes quaternary ammonium groups formed at the 3-position of cephem ring, such as pyridinium, quinolinium, isoquinolinium and pyrimidinium. In this case, a betaine structure is formed in the molecule. 30

In the general formula (I), m pairs of R² and R³, which may be the same or different, represent individually, a hydrogen atom; a halogen atom such as fluorine, chlorine or bromine; a carboxyl group; an alkyl group such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl; a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl; an aryl group such as phenyl or naphthyl; an acyl group such as acetyl, propionyl, butyryl or benzoyl; an aralkyl group such as benzyl or phenethyl; an alkoxycarbonylalkyl group such as methoxycarbonylmethyl or ethoxycarbonylmethyl; an acyloxyalkyl group such as methoxycarbonylmethyl, propionyloxymethyl; an alkoxycarbonyl group such as methoxycarbonyl, ethoxy, propoxy or butoxy; an alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl; an aralkoxycarbonyl, ethoxycarbonyl, cyclohexyloxycarbonyl or cycloheptyloxycarbonyl; an aralkoxycarbonyl group such as benzyloxycarbonyl or cycloheptyloxycarbonyl; an aralkoxycarbonyl group such as benzyloxycarbonyl or phenethoxycarbonyl; an aryloxycarbonyl group such as phenoxycarbonyl or naphthoxycarbonyl; an amino group such as amino, N-alkylamino (e.g. N-methylamino, N-ethylamino, N-Propionylamino, N-butyrylamino or N-benzoylamino), and cyclic amino (e.g. pyrrolidino, piperidino, or morpholino); and a carbamoyl group such as carbamoyl, N-methylamino-carbonyl, N-ethylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methylaminocarbonyl, N-ethylaminocarbonyl, N,N-dimethylaminocarbonyl, N-methylaminocarbonyl, N-methylaminocarbonyl, N-methylaminocarbonyl, N-ethylaminocarbonyl, N-methylaminocarbonyl, N-me

In the general formula (I), A represents a hydrogen atom; a hydroxy group; a nitro group, a cyano group; an alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, or dodecyl; an alkenyl group such as vinyl, propenyl or butenyl; an alkynyl group such as propargyl; an alkadienyl group such as 1,3-butadienyl or 1,3-pentadienyl; a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl; a cycloalkenyl group such as cyclopentenyl or cyclohexenyl; a cycloalkadienyl

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thoyloxy, cyclopentanecarbonyloxy, cyclohexanecarbonyloxy, furoyloxy or thenoyloxy; carbamoyloxy groups such as carbamoyloxy, N-methylaminocarbonyloxy, N,Ndimethylaminocarbonyloxy, N-acetylaminocarbonyloxy, phenylaminocarbonyloxy, benzylaminocarbonyloxy or cyclohexylaminocarbonyloxy; guanidino groups such as phenylaminocarbonyloxy, guanidino or N-methylguanidino; amino groups such as amino, N-alkylamino (e.g. N-methylamino, N-ethylamino, N-propylamino, N-butylamino, N-cyclohexylamino or Nphenylamino), N,N-dialkylamino (e.g. N,N-dimethylamino, N,N-diethylamino or

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N,N-dibutylamino), and cyclic amino (e.g. pyrrolidino, piperidino or morpholino); alkylthio groups such as methylthio, ethylthio or propylthio; arylthio groups such as phenylthio or (1- or 2-)naphthylthio; aralkylthio groups such as benzylthio or phenethylthio; acylthio groups such as acetylthio, propionylthio, butyrylthio, benzoylthio, (1- or 2-)naphthoylthio, cyclopentanecarbonylthio, cyclohexanecarbonylthio, furoylthio, thenoylthio, isothiazolecarbonylthio, isoxazolecarbonylthio, thiadiazolecarbonylthio or triazolecarbonylthio; thiocarbamoylthio groups such as thiocarbamoylthio, N-methylthiocarbamoylthio, N,N-diethylthiocarbamoylthio, 1-piperidino-thiocarbonylthio, 1morpholinothiocarbonylthio or 4-methyl-1-piperazinothiocarbonylthio; alkoxythiocarbonylthio groups such as methoxythiocarbonylthio, ethoxythiocarbonylthio, propoxythiocarbonylthio or butoxythiocarbonylthio; aryloxythiocarbonylthio groups such as phenoxythiocarbonylthio; cycloalkyloxythiocarbonylthio groups such as cyclohexyloxythiocarbonylthio; amidinothio groups such as amidinothio, N-methylamidinothio or N,N'-dimethylamidinothio; and heterocyclic thio groups such as oxazolylthio, thiazolylthio, isoxazolylthio, isothiazolylthio, imidazolylthio, pyrazolylthio, pyridylthio, pyrazinylthio, pyrimidinylthio, pyridazinylthio, quinolylthio, isoquinolylthio, quinazolylthio, indolylthio, indazolylthio, oxadiazolylthio, thiadiazolylthio, triazolylthio, tetrazolylthio, triazinylthio, benzimidazolylthio, benzoxazolylthio, benzothiazolylthio, triazolopyridylthio, purinylthio, pyridine-1-oxide-2-ylthio or pyridazine-1-oxide-6-ylthio. Each of the groups mentioned above for R4 may be substituted by any of such substituents as, for example, halogen atoms, alkyl groups, alkoxy groups, alkylthio groups, nitro groups, cyano groups, acylamino groups, acyl groups, carboxyl groups or carbamoyl groups.

The above-mentioned compounds of formula (I) of the present invention have their optical isomers, and all of D-isomers, L-isomers and racemic compounds thereof

are involved in the scope of the present invention.

In the present invention, preferable compounds of the general formula (I) are as follows:

$$A - N \longrightarrow N - C - NH - CH - CONH \longrightarrow N \longrightarrow Z$$

$$(Ia)$$

$$(R^2 - R^3)_3 \longrightarrow R^5$$

$$COOR^1$$

$$A-N \longrightarrow 0 \qquad C-NH-CH-CONH \longrightarrow S \qquad (Ie)$$

$$(R^2 R^3_2) \qquad R^5 \qquad COOR^1$$

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are as defined above.

The compounds of formula (I) of the present invention are produced according to either the process (1), (2) or (3) described below.

Process (1):

A process comprising reacting a compound represented by the general formula (II),

$$R^7-NH-R-CONH$$

$$0$$

$$COOR_1$$
(III)

with a reactive derivative in the 10

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group (hereinafter refered to as "(thio)carboxyl group") of a compound represented by the general formula (III),

$$A - N - C - OH$$

$$(R^2 R^3)_{M}^{N} Y$$
(111)

Process (2): 15 A process comprising reacting a compound represented by the general formula 15

with a compound represented by the general formula (V),

or with a reactive derivative in the

group (hereinafter referred to as "carboxyl group") of the compound of formula (V).

25 Process (3): 25 A process comprising reacting a compound represented by the general formula (VI),

with a compound represented by the general formula (VII),

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	R ^s M (VII)	<u>A</u>
	or with a tertiary amine. In the above-mentioned formulas (II) to (VI), R, R ¹ , R ² , R ³ , R ⁴ , X, m, n, A, Y	. -
5	and	5
	\	
	z	
	V	
	are as defined above; and R' represents a hydrogen atom, a silicon-containing group or	
	a phosphorus-containing group, these silicon-containing and phosphorus-containing groups having the same meanings as mentioned above for R ¹ .	10
10	In the aforesaid formula (VI), B represents a substituent capable of being easily	
	replaced by a nucleophilic reagent, and includes, for example, halogen atoms such as	
	chlorine of bromine; lower alkanoyloxy groups such as formyloxy, acetoxy, propionyloxy, butyryloxy or pivaloyloxy; arylcarbonyloxy groups such as benzoyloxy or naph-	
	thoyloxy; arylcarbonylthio groups such as benzoylthio or naphthoylthio; carbamoyloxy	15
15	groups; heteroaromatic amine N-oxide this groups having a this-group on the carbon	
	atom adjacent to the N-oxide group in the molecule, such as pyridine-1-oxide-2-ylthio or pyridazine-1-oxide-6-ylthio. Each of the groups mentioned above for B may be sub-	
	stituted by any of such substituents as, halogen atoms, nitro groups alkyl groups, alkoxy	20
20	groups, alkylthio groups or acyl groups. In formula (VII), R ⁸ represents a cyano group, an azido group or an organic	20
20	group linked through O, N or S, and this organic group is the same as mentioned above	
	for R ⁴ .	
	In the formula (VII), M represents a hydrogen atom, an alkali metal or an alkaline earth metal. The tertiary amine used in the process (3) includes pyridine, quinoline,	25
25	isoquinoline or pyrimidine. These tertiary amines may be substituted by various substi-	
	tuents such as halogen, lower alkyl or carbamoyl. As the compound (II), there may be used any of D-isomer, L-isomer or racemic	
	compound.	
30	As the reactive derivative of the (thio)carboxyl group of the compound of formula	30
30	(II), there is used a reactive derivative of a carboxylic acid which is ordinarily employed for the synthesis of acid amide compounds. Examples of the reactive deriva-	
	tive are acid halides, acid azides, acid cyanides, mixed acid anhydrides, active esters or	
	active amides. Particularly preferable examples thereof are acid halides such as acid chlorides or acid bromides, and active esters such as cyanomethyl ester or trichloro-	35
35	methyl ester.	
	The reactive derivative of the (thio)carboxyl group of the compound of formula	
	(III) can be easily obtained by reacting, for example, an oxopiperazine or thioxopiper- azine of formula (VIII) synthesized according to the process of the literature references	
40.	described below, with phosgene, thiophosgene, or trichloromethyl ester of chloroformic	40
40	acid,	
	(x) _n	
	A-N NH (VIII)	,
	(R2: R3) _m	
	wherein A, X, R ² , R ³ , m and n are as defined previously.	ě
	Literature references:	ŝ
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50	Jongkees, Rec. trav. Chim., 27 305;	
50	Patric T. Izzo, J. Am. Chem. Soc., 81 4668—4670 (1959); and B. H. Chase & A. M. Downes, J. Chem. Soc., 3874—3877 (1953).	50
	Concrete examples of the compound of formula (VIII) and the reactive derivative	•
	of (thio)carboxyl group of the compound of formula (III) are as set forth in Table 1 and Table 2, respectively, but it is needless to say that these are not limitative.	
		•

Table 1

Compound	m.p. (recry- stallization solvent)	IR (cm ⁻¹)	
O HN NH	136°C ((0))	$V_{C=0}$ 1640 V_{NH} 3450 - 3250	
O CH3 HN NH	b.p. 143 ^o C/l mmHg oily material	$V_{C=0}$ 1650 V_{NH} 3300 - 3200	
O HN NH CH ₃	b.p. 122 - 125°C/2 mmHg 140 - 141°C (IPA)		
O CH ₃ HN NH CH ₃	85 - 86°C (IPA - IPE)	ν _{C=0} 1660 - 1620	
о сн ₂ со ₂ с ₂ н ₅ ни ин	105 - 106 ⁰ C (Ac0Et)	$ \lambda_{C=0} $ 1710, 1640 $ \lambda_{NH} $ 3300, 3190	
O CH3CON NH	112 - 113°C (🔘)	$V_{C=0}$ 1645, 1625 V_{NH} 3380, 3220	
C1CH2CON NH	129 - 130 ⁰ C (IPA)	$y_{C=0}$ 1650, 1630 y_{NH} 3270	

- cont'd -

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Table 1 (Cont'd)

		,
C12CHCON NH	134 - 135°C (IPA)	ν _{C=O} 1660-1630 ν _{NH} 3280
CH ₃ (CH ₂) ₁₃ CH ₂ CON NH	96 - 97°C (CC1 ₄)	$V_{C=0}$ 1670, 1640 V_{NH} 3200
CH ₃ (CH ₂) ₅ CH ₂ CON NH	80 - 81 ⁰ C (IPE)	√ _{C=0} 1660, 1620 √ _{NH} 3250
CH ₃ (CH ₂) ₄ CH ₂ CON NH	83 - 84°C (IPE)	$v_{\rm C=0}$ 1660, 1620 $v_{\rm NH}$ 3250
CH ₃ (CH ₂) ₃ CH ₂ CON NH	99 - 100°C (CC1 ₄)	ν _{C=O} 1660, 1620 ν _{NH} 3250
O (H)— CON_NH	203 - 205 ⁰ C (IPA)	√ _{C=0} 1670, 1620 √ _{NH} 3250
O CON NH	91 - 93 ⁰ C (IPA)	$ \sqrt{_{\text{C=0}}} $ 1640, 1600 $ \sqrt{_{\text{NH}}} $ 3250
C1-(O)-CON NH	146 - 148 ⁰ C (IPA)	$\sqrt{_{\text{C=0}}}$ 1650, 1620 $\sqrt{_{\text{NH}}}$ 3200
CH3-O-CON_NH	118 - 120 ⁰ C (IPA)	Υ _{C=0} 1660, 1620 √ _{NH} 3200
CH ₃ 0 0 CH ₃ 0 CON NH CH ₃ 0	182 - 185 ⁰ C (IPA)	ν _{C=0} 1670, 1600 ν _{NH} 3200

Table 1 (Cont'd)

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C1 O C1-O-CON NH	Oily material	ν _{C=O} 1650, 1620 ν _{NH} 3200
CH3 O CH3CON NH	124 - 126°C (O)	$V_{C=0}$ 1650, 1630 V_{NH} 3225
O CH ₃ SO ₂ N NH	167 - 168°C (EtOH)	V _{C=0} 1680 V _{NH} 3200 V _{SO2N<} 1310, 1140
CH3CONHCON NH	176 - 179°c (🔘)	$V_{C=0}$ 1680, 1650, 1620
O-nhcon nh	85 - 88°C (AcOEt)	ν _{C=0} 1660, 1640 ν _{NH} 3300, 3200
CH3CH2OCON NH	81 - 82°C ((0))	$ \sqrt[4]{_{\text{C=0}}} $ 1690 - 1650 $ \sqrt[4]{_{\text{NH}}} $ 3200, 3050
Сн ₃) ₃ со-осн ₂ -и ин	189 - 190°C (IPA)	$V_{C=0}$ 1650, 1620 V_{NH} 3250
O O HN NH	136 - 138°C (Acetone)	√ _{C=0} 1660 √ _{NH} 3200
CH ₃ (CH ₂) ₄ CH ₂ -N NH	Oily material	ν _{C=0} 1650 - 1630 ν _{NH} 3270
CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	V _{NH} 3250 V _{C=0} 1650 - 1630

Table 1 (Cont'd)

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CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	ν _{C=0} 1650 - 1620
CH ₃ (CH ₂) ₆ CH ₂ -NNH	Oily material	$V_{\rm NH}$ 3270 $V_{\rm C=0}$ 1650 - 1630 Hydrochloride $V_{\rm C=0}$ 1680 $V_{\rm NH}$ 3200, 3080
O CH ₃ CH ₃ CON NH	Oily material	ν _{C=O} 1680 ν _{NH} 3300
O_NHCON_NH	Oily material	$V_{C=0}$ 1720, 1640 V_{NH} 3300
CH3N NH	b.p. 104 ⁰ C/4 mmHg	V _{C=O} 1620 V _{NH} 3275
CH ₃ CH ₂ -NNH	Oily material	V _{C=0} 1610 V _{NH} 3250
CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	V _{C=0} 1610 V _{NH} 3250
о (сн ₃) ₂ сн-и ин	Oily material	ν _{C=O} 1610 ν _{NH} 3400 - 3200
CH ₃ (CH ₂) ₃ CH ₂ -N NH	Oily material	ν _{C=O} 1620 ν _{NH} 3270
CH ₃ CHCH ₂ CH ₂ -N NH	Oily material	ν _{C=0} 1620 ν _{NH} 3270

- cont'd .

Table 1 (Cont'd)

ŧ		
о сн ₃ (сн ₂) ₄ сн ₂ -и ин	Oily material	ν _{C=0} 1620 ν _{NH} 3270
сн ₃ (сн ₂) ₅ сн ₂ -и ин	Oily material	√ _{C=0} 1620 √ _{NH} 3270
CH ₃ (CH ₂) ₆ CH ₂ -N NH	Oily material	√ _{C=0} 1620 √ _{NH} 3270
о сн ₃ (сн ₂) ₁₀ сн ₂ -и ин	Oily material	ν _{C=0} 1620 ν _{NH} 3270
H)—N NH	Oily material	√ _{C=0} 1620 √ _{NH} 3300
O CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	ν _{C=0} 1630 ν _{NH} 3300
CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	√ _{C=O} 1630 √ _{NH} 3300
CH ₃ (CH ₂) ₂ CH ₂ -N NH	Oily material	ν _{C=0} 1630 ν _{NH} 3200
O-CH ₂ -N NH	157 - 158°c ([0])	ν _{C=0} 1630 ν _{NH} 3300

Table 1 (Cont'd)

O CH ₃ H ₂ NCO-N NH	Oily material	$V_{C=0}$ 1700 V_{NH} 3400 - 3250
HOCH ₂ CH ₂ -N NH	b.p. 183-185 ⁰ C/2mmHg	ν _{C=0} 1620
O CH ₂ =CHCH ₂ -N NH	Oily material	√ _{C=0} 1650 √ _{NH} 3300
CH ₂ =CHCH-N NH CH ₃	Oily material	√ _{C=0} 1620 √ _{NH} 3300
CH ₂ =CCH ₂ -N NH CH ₃	Oily material	ν _{C=0} 1640 ν _{NH} 3300
CH=CHCH ₂ -N NH CH ₃	Oily material	√ _{C=0} 1660 √ _{NH} 3350
ONCH2-N NH	Oily material	ν _{C=0} 1630 ν _{NH} 3300
CH3CO-N NH	184 - 185 ⁰ C (EtOH)	$V_{\rm C=0}$ 1690 - 1650 $V_{\rm NH}$ 3190, 3050
O-con NH	177 - 178 ⁰ C (EtoH)	$V_{C=0}$ 1680 - 1650 V_{NH} 3190, 3050

- contid

Table 1 (Cont'd)

CH ₃ -N NH	142 - 143°C (IPA)	ν _{C=0} 1680 – 1620 ν _{NH} 3200
O-cH ₂ -N-NH	209°C (IPA)	$V_{C=0}$ 1660 - 1630 V_{NH} 3230
O O CH ₃ -N NH	158 ^O C (IPA)	ν _{C=O} 1695, 1660 ν _{NH} 3220
O O CH3COOCH2CH2-N NH	Oily material	$\sqrt{C_{=0}}$ 1730 - 1650 \sqrt{NH} 3300 - 3200
CH3CH2-N NH	124°C ((0))	$V_{C=0}$ 1680, 1650 V_{NH} 3250
O O CH3CH2CH2-N NH	98 - 100°C ((°))	$V_{\rm C=0}$ 1680, 1650 $V_{\rm NH}$ 3200, 3100
O O CH ₃ (CH ₂) ₂ CH ₂ -N NH	111 - 113°C (CCl ₁₊)	$V_{C=0}$ 1695, 1670 V_{NH} 3240, 3150
O O (CH ₃) ₂ CH-N NH	166 - 167°C ((0))	V _{C=0} 1650 V _{NH} 3300 - 3200
O O CH ₃ (CH ₂) ₃ CH ₂ -N NH	104 - 106 ⁰ C (IPE)	$V_{C=0}$ 1700, 1660 V_{NH} 3200, 3100
O O CH ₃ (CH ₂) ₄ CH ₂ -N NH	111 - 115°C (IPE)	$V_{C=0}$ 1700, 1660 V_{NH} 3200, 3100

Table 1 (Cont'd)

	<u>.</u>	·
о о ch ₃ (ch ₂) ₅ ch ₂ -n nh	112 - 115°C (IPE)	$V_{C=0}$ 1700, 1660 V_{NH} 3200, 3100
о о сн ₃ (сн ₂) ₆ сн ₂ –и мн	116 - 120°C (IPE)	$V_{C=0}$ 1700, 1660 V_{NH} 3225, 3100
O O CH ₂ =CHCH ₂ -N NH	136 - 137°C (Acetone)	ν _{C=0} 1680, 1655 ν _{NH} 3200, 3100
O O N NH	202 - 204 ⁰ C (IPA)	$V_{C=0}$ 1690, 1645 V_{NH} 3260
C1CH ₂ CH ₂ N NH	128 - 129 ⁰ C (EtOH)	$V_{C=0}$ 1700 - 1650 V_{NH} 3200 - 3100
O O CH3CH2-N NH CH3	127 - 128 ⁰ C (AcOEt)	$V_{C=0}$ 1660 V_{NH} 3200, 3080
O O CH3-N NH CH3	146 - 147°C ((0))	$V_{C=0}$ 1660 V_{NH} 3200, 3100
O H NH	183 — 185 ⁰ С (Еtон)	ν _{C=0} 1720, 1660 ν _{NH} 3320, 3175, 3050
O-cH ₂ -N NH	96 - 99 ⁰ C . (IPA-n-Hexane)	ν _{C=O} 1720, 1660 ν _{NH} 3330

Table 1 (Cont'd)

Cl ₃ CCH ₂ OCO-N NH	143 - 146°C (IPA)	ν _{C=0} 1765, 1720, 1680 ν _{NH} 3350
O HN NH O	210 - 212 ⁰ C (MeOH)	V _{C=0} 1680 V _{NH} 3380, 3290, 3070
OCH3 HN NH	132 - 133°C (EtOH)	ν _{C=0} 1715, 1685 ν _{NH} 3275, 3170
OCH ₂ -N NH	98 - 100°C (IPA)	V _{C=0} 1715, 1665 V _{NH} 3360

Note: IPA = $(CH_3)_2CHOH$

IPE = $(CH_3)_2CHOCH(CH_3)_2$

AcOEt = CH3COOCH2CH3

EtoH = CH₃CH₂OH

,

Table 2

Reactive derivatives of A-N N-COH (III)
$$(R^2R^3)_m$$

Compound	Physical property	I.	R. (cm ⁻¹)
o ch ₃ co-n n-cocl	Oily material	$V_{C=0}$	1790, 1710, 1640
O ClCH ₂ CO-N N-COCl	11	ν _{C=0}	1790, 1730 - 1650
Cl ₂ CHCO-N N-COCl	"	. Y _{C=0}	1790, 1730 - 1650
CH ₃ (CH ₂) ₁₃ CH ₂ CO-N N-COC	:1 " [λ _{C=0}	1740, 1660, 1640
CH ₃ (CH ₂) ₅ CH ₂ CO-N N-COC1	п	√ _{C=0}	1740, 1680 - 1640
CH ₃ (CH ₂) ₄ CH ₂ CO-N N-COC1	"	√ _{C=0}	1740, 1680 - 1640
CH ₃ (CH ₂) ₃ CH ₂ CO-N N-COC1		√ _{C=0}	1790, 1710, 1640

Table 2 (Cont'd)

j		
H CO-N N-COC1	Oily material	ν _{C=0} 1790, 1730,
o O-co-n n-cocl	. "	ν _{C=0} 1740, 1660, 1630
CIO-CO-N N-COCI		ν _{C=0} 1740, 1640
0 CH ₃ -(O)-CO-N N-COC1	"	ν _{c=0} 1730, 1650
CH ₃ O O CH ₃ O CH ₃ O	11	√ _{C=0} 1740, 1640
C1 O C1-O-CO-N N-COC1	"	V _{C=0} 1720, 1640
CH3 O CH3CO-N N-COC1	n	V _{C=0} 1790, 1710,
o ch ₃ so ₂ -n n-coc1		$ \sqrt[4]{c_{=0}} $ 1790, 1700 $ \sqrt[4]{so_2} $ 1320, 1140
CH3CONHCO-N N-COC1	п	V _{C=0} 1790, 1720 - 1660

Table 2 (Cont'd)

_		
O-NHCO-N N-COC1	Oily material	ν _{C=0} 1740, 1720,
CH3CH2OCO-N N-COC1	11	ν _{C=0} 1750, 1720, 1640
(CH ₃) ₃ CCOOCH ₂ -N N-COC1	ti	√ _{C=0} 1740 - 1720, 1670
CH ₃ (CH ₂) ₄ CH ₂ -N N-COC1	11	√ _{C=0} 1790, 1720
O CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	t t	√ _{C=0} 1790, 1720
CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	11	ν _{C=0} 1790, 1720
CH ₃ (CH ₂) ₆ CH ₂ -N N-COC1	11	ν _{C=0} 1790, 1720
O HN N-COC1	m.p. 115 - 116°C (decomp.) (from ())	ν _{C=0} 1720, 1660
O CH3 HN N-COC1 CH3	Crystal	√ _{C=0} 1730, 1670

Table 2 (Cont'd)

	•	·
O HN_N-COC1 CH ₃	Crystal	√ _{C=0} 1720, 1660
O CH ₂ COOCH ₂ CH ₃ HN N-COC1	m.p. 59 - 60 ⁰ C (from IPE)	√ _{C=0} 1710 - 1730, 1660
O CH ₃	m.p. 98 - 100°C (from O)	ν _{C=0} 1725, 1650
O CH ₃ CH ₃ CO-N N-COC1	Oily material	√ _{C=0} 1720, 1690
O-NHCO-N N-COCI	n	ν _{C=0} 1790, 1740 - 1700
O CH3-N N-COC1	n	ν _{C=0} 1710, 1630
о сн ₃ (сн ₂) ₂ сн ₂ -и и-сос1	II .	ν _{C=0} 1730, 1650
O CH ₃ CH ₂ -N N-COC1	11	ν _{C=0} 1730, 1650
0 (CH ₃) ₂ CH-N N-COC1	11	√ _{C=0} 1720, 1640

Table 2 (Cont'd)

CH ₃ (CH ₂) ₃ CH ₂ -N N-COC1	Oily material	√ _{C=0} 1730, 1640
(CH ₃) ₂ CHCH ₂ CH ₂ -N N-COC1	"	ν _{C=0} 1720, 1640
CH ₃ (CH ₂) ₄ CH ₂ -N N-COC1	11	√ _{C=0} 1730, 1640
CH ₃ (CH ₂) ₅ CH ₂ -N N-COC1	11	√ _{C=0} 1730, 1640
CH ₃ (CH ₂) ₆ CH ₂ -N N-COC1	11	√ _{C=0} 1720, 1640
CH ₃ (CH ₂) ₁₀ CH ₂ -N N-COC1	11	ν _{C=0} 1720, 1640
O H)-N_N-COC1	"	γ _{C=0} 1730, 1640
O CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	11	√ _{C=0} 1730, 1640
CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	ti	√ _{C=0} 1720, 1640

Table 2 (Cont'd)

CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1	Oily material	γ _{C=0} 1730, 1650
HN_N-COCI	m.p. 105 - 107°C	√ _{C=0} 1730, 1650
O CH ₂ -N N-COC1	Oily material	ν _{C=0} 1720, 1645
O CH ₃ H ₂ NCO-N N-COC1	11	√ _{C=0} 1700 - 1740
HOCH2CH2-N N-COCI	П	√ _{C=0} 1730, 1660 - 1630
O CH ₂ =CHCH ₂ -N N-COC1	11	V _{C=0} 1720, 1640
CH ₂ =CHCH-N N-COC1	п	√ _{C=0} 1730, 1650
CH ₂ =CCH ₂ -N N-COC1 CH ₃	,,	ν _{C=0} 1730, 1650

Table 2 (Cont'd)

CH ₃ CH O CHCH ₂ -N N-COC1 (trans-)	Oily material	ν _{c=0} 1730, 1650
O N-CH ₂ -N N-COC1	m.p. 150 ⁰ C (decomp.)	√ _{C=0} 1670, 1720
0 CH3CO-N N-COC1	Oily material	ν _{C=0} 1790, 1720 - 1670
O CO-N N-COC1	11	ν _{C=0} 1790, 1710,
O CH ₃ -N N-COC1 O	II	ν _{C=O} 1790, 1710 - 1660
O CH ₂ -N N-COC1	ıı .	√ _{C=0} 1790, 1710 - 1660
O O CH3-N N-COC1	m.p. 94 - 95°C (decomp.) (from CH ₂ Cl ₂ - Et ₂ O)	√ _{C=0} 1790, 1680
CH3COOCH2CH2-N N-COCI	Oily material	√ _{C=0} 1790, 1720, 1670

Table 2 (Cont'd)

o o ch ₃ ch ₂ -n n-cocl	m.p. 95 - 96 ⁰ C (decomp.) (from AcOBu)	ν _{C=0} 1780, 1660
O O CH3CH2CH2-N N-COC1	Oily material	ν _{C=0} 1780, 1710 - 1640
CH3(CH ⁵) ⁵ CH ⁵ -N N-COCI	11	ν _{C=0} 1780, 1660
0 0 V—((CH ₃) ₂ CH-N N-COC1	m.p. 130 - 131°C (decomp.)	ν _{c=0} 1780, 1660
O O CH ₃ (CH ₂) ₃ CH ₂ -N N-COCl	Oily material	ν _{C=0 1790} , 1720 - 1665
CH ₃ (CH ₂) ₄ CH ₂ -N N-COCL	et .	V _{C=0} 1780, 1720 → 1640
O O CH ₃ (CH ₂) ₅ CH ₂ -N N-COC1		ν _{C=0} 1780, 1720 - 1640
CH ₃ (CH ₂) ₆ CH ₂ -N N-COC1	11	√ _{C=0} 1780, 1720 - 1640
O O CH ₂ =CHCH ₂ -N N-COC1	Crystal	V _{C=0} 1775, 1660 - 1620

Table 2 (Cont'd)

O O N_N-COC1	Crystal	λ _{C=0}	1785, 1720 – 1650
O O O N-COCI	Oily material	$\lambda^{c=0}$	1790, 1720, 1680
0 0 CH ₃ CH ₂ -N N-COC1 CH ₃	m.p. 65 - 70 ⁰ C (decomp.)	√ _{C=0}	1785, 1680
O O CH3CH2-N N-CSC1	m.p. 100 - 101°C (decomp.)	√ _{C=0}	1725, 1675
O H HN N-COC1	m.p. 180 - 181 ⁰ C	ν _{C=0}	1740, 1695
O H O-CH ₂ -N N-COC1	m.p. 160 - 165 ⁰ С	√ _{C=0}	1740, 1670
Cl ₃ CCH ₂ OCO-N N-COCl	Oily material	√ _{C=0}	1800, 1750, 1710

25

Table 2 (Cont'd)

O N-COCL	m.p. 185 - 187 ⁰ C (decomp.)	√ _{C=0} 1730, 1690
OCH3 HN N-COC1	Oily material	√ _{C=0} 1750, 1710 - 1685
OCH ₂ -N N-COC1		V _{C=0} 1735, 1725, 1710, 1675

Note: $Et_2O = CH_3CH_2OCH_2CH_3$ $AcOBu = CH_3COO(CH_2)_3CH_3$

The compound represented by the general formula (V) can be easily obtained by reacting, for example, a salt with an alkali metal, an alkaline earth metal or a nitrogencontaining organic base of an amino acid (IX) (any of D-isomer, L-isomer and racemic compound) represented by the general formula (IX)

 H_2N —R—COOH (IX)

wherein R is as defined previously, with a reactive derivative in the (thio)carboxyl group of a compound represented by the general formula (III) in a solvent inert to the reaction in the presence of an acid-binding agent. Preferable examples of the compound of formula (V) are D-isomers, L-isomers and racemic compounds of the following 10 10 compounds, though it is needless to say that the examples are not limitative: α - (4 - Acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - Chloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - Dichloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid 15 α - (4 - Palmitoyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid 15 α - (4 - Caproyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Capryloyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Enanthoyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Cyclohexanecarbonyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid 20 acetic acid 20 (4 - Benzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid - p - Chlorobenzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic α - (4 - p - Methoxybenzoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetic 25

_28	1,500,5002	20	
	α - [4 - (3,4,5 - Trimethoxybenzoyl) - 2 - 0x0 - 1 - piperazinocarbonylamino]-		
	phenylacetic acid α - [4 - (2,4 - Dichlorobenzoyl) - 2 - οχο - 1 - piperazinocarbonylamino] phenyl-		Ţ
5	acetic acid $\alpha - (4 - Acetyl - 3 - methyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic$	5	
	acid α - (4 - Methanesulfonyl - 2 - οχο - 1 - piperazinocarbonylamino)phenylacetic	=	*
	acid α - (4 - Acetylaminocarbonyl - 2 - οχο - 1 - piperazinocarbonylamino)phenylacetic	10	
10	acid α - (4 - Phenylaminocarbonyl - 2 - οχο - 1 - piperazinocarbonylamino)phenyl-	10	
	acetic acid α - (4 - Ethoxycarbonyl - 2 - οχο - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - Pivaloyloxymethyl - 2 - οχο - 1 - piperazinocarbonylamino)phenylacetic	15	
15	acid $\alpha - (4 - n - \text{Hexyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid $\alpha - (4 - n - \text{Butyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic acid $\alpha - (4 - n - \text{Butyl} - 6 - \text{methyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenyl-	15	
20	acetic acid α - (4 - n - Octyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (3 - Oxo - 1 - piperazinocarbonylamino) phenylacetic acid	20	
	 α - (2,5 - Dimethyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (5 - Methyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (2 - Ethoxycarbonylmethyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacetic acid 	25	,
25	α - (2 - Methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - Acetyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic		_
	acid α - (4 - Phenylaminocarbonyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl- acetic acid	30	- '
30	actic acid $\alpha = (4 - Methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid \alpha = (4 - n - Butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid \alpha = (4 - Ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid \alpha = (4 - Isopropyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid$		-
35	α - (4 - 1sopropyl - 3 - 0x0 - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - n - Pentyl - 3 - 0x0 - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - n - Hexyl - 3 - 0x0 - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - n - Heptyl - 3 - 0x0 - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - n - Heptyl - 3 - 0x0 - 1 - piperazinocarbonylamino)	35	
40	α - (4 - n - Neptyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - n - Dodecyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - n - Dodecyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (2 - Methyl - 4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-	40	
45	acetic acid $\alpha - (4 - n - Butyl - 5 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid \alpha - (4 - n - Butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid$	45	
50	acetic acid $\alpha - (2 - Phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid \alpha - (4 - Benzyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid \alpha - (4 - Carbamoyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid \alpha - (4 - \beta - Hydroxyethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic$	50	
55	acid $\alpha - (4 - \text{Allyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) \text{ phenylacetic acid}$ $\alpha - (4 - \alpha - \text{Methylallyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) \text{ phenylacetic acid}$ $\alpha - (4 - \beta - \text{Methylallyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) \text{ phenylacetic acid}$ $\alpha - [4 - (\text{Trans} - 2 - \text{butenyl}) - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino}] \text{ phenylacetic acid}$	55	÷- •
60	acetic acid $\alpha - (4 - Morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid$	60	
UV	α - (4 - Ethyl - 3 - oxo - 1 - piperazinocarbonylamino) propionic acid α - (4 - Acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Benzoyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid α - (4 - Methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid	٠.	
65	α - (4 - Benzyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid	. 65	

29	1,500,002	
	α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid α - (4 - Acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic	,
	acid	
=	α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid	5
້5	- A - n - Propul - 2.3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid	. J
•	- (4 - n - Butyl - 2.3 - dioxo - 1 - piperazinocarbonylamino) pnenylacetic acid	
	a = (4 = Isopropyl = 2.3 = dioxo = 1 = piperazinocarbonylamino) phenylaceuc acid	
2	= 1/4 - n - Pentul - 2.3 - dioxo - 1 - niperazinocarbonylamino) phenylacetic acid	
		10
10	- A - n - Hentyl - 2.3 - dioxo - 1 - piperazinocarbonylamino) pnenylacelic acid	10
	- A - p - Octul - 23 - d oyo - 1 - ninerazinocarponylamino) pnenylacetic acid	
	- /A Allyl - 23 - dioxo - 1 - ninerazinocarbonylamino) phenylacetic acid	
	(A Dhenril - 23 - diogo - 1 - hinerazinocarponviamino innenviacene acid	
	$\alpha - (4 - \beta - \text{Chloroethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetic	
15	anid	15
1.5	α - (4 - Pyrrolidinoethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic	
	aaid	
	α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenyl-	
	aceta poid	
20	α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenyl-	20
20	annia acid	
	α - (6 - Methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	
	anatia naid	
	(4.6. Dimethyl - 2.3 - diovo - 1 - piperazinocarbonylamino) phenylacetic acid	
25	// Pthyl 22 diogo - 1 - ninerazinotniocarponyiamino i pilettylacette actu	25
25	α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexa-	
	diannilocatio coid	
	α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexadienyl-	
	anatic said	
	α - (4 - n - Propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexa-	30
30	diamelacatic acid	
	α - (4 - n - Butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4 - cyclohexa-	
	diamile cation acid	
	α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic	
25	acid	35
35	α - (4 - Ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic acid	
	$\alpha = (4 - n - \text{Propyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - 2 - \text{thienylacetic}$	
	!J	•
	acid α - (4 - n - Butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienylacetic	
40	acid	40
40	α - (2,2 - Pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-	_
	acetic acid	
	α - (4 - Benzyl - 2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonyl-	
	amino) phenylacetic acid	
AE	$\alpha - (4 - \beta_1\beta_1\beta_1\beta_2)$ - Trichloroethoxycarbonyl - 2,2 - pentamethylene - 3,5 - dioxo - 1-	45
45	piperazinocarbonylamino)phenylacetic acid	
	/2 5 Diovo _ 1 _ ninerazinocarhonvlamino \nnenvlacelic acid	
	$\alpha = (3.5 - \text{Diox}) - 1 - \text{piperazinocarbonylamino}$ phenyl- $\alpha = (2 - \text{Methyl} - 2 - \text{phenyl} - 3.5 - \text{diox} - 1 - \text{piperazinocarbonylamino})$ phenyl-	
	anatia anid	
50	α - (4 - Benzyl - 2 - methyl - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-	50
30	antia anid	•
	α - (4 - Methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetic acid	
*	As the reactive derivative in the carboxyl group of the compound represented by	
	the general formula (V), there is used a reactive derivative of a carboxylic acid which	
	is addingely used in the conthesis of said smides. Such reactive gerivative includes, for	55
55	annual acid bolides acid approprides mixed acid approprides with organic or morganic	
•	aside active acid emidee acid evanides of active esters. Particularly, acid chloraces,	
	mired said appropriates and active acid amides are preferable. Examples of the mace	
	and an Ludaidae are mixed acid appropriates with supstituted acetic acids, alkyl carbonic	
	acide and combonic acide and arally carbonic acids: examples of the active esters are	60
60		
	thienyl esters; and examples of the active acid amides are N-acyl saccharins, N-acyl	
	imidazoles, N-acyl benzoylamides, N,N-dicyclohexyl-N-acylureas or N-acyl	
	Ifanomidos	
	sulfonamides. Compounds of formula (VI) can be obtained by, for example, process (1) or (2).	65
65	Comboding of forming (A1) can be enquired 533 and are Last Last A 1 x x x x	

	Some of the compounds obtained by process (3) can further be used as the starting compounds in process (3). Any of D-, L- and racemic compounds of formula (VI)	à
	may be used.	
	The modes of practice of the processes (1), (2) and (3) are explained below.	5
5	The menacone (1) and (7) may be carried all lieuer substantially the same con	J
J	That is the compound of formula (11) of (1V) is dissolved of suspended in ac	2
	1 inch column colorion from the pasifilities waters account without account	a.
	1	
	ether, isopropyl ether, benzene, toluene, methylene chloride, chloroform, ethyl acetate	•
	and methyl isobutyl ketone. The resulting solution or suspension is reacted with a reac-	10
10	and methyl isobutyl ketone. The resulting solution is an arish the compound of formula	
	tive derivative of the compound of formula (III), or with the compound of formula tive derivative of the compound of formula (V) in	•
	at a manage of a broad of a base at a reminerality in the language from	
		•
	The state of the bace used in the above reaction are indigatic dates such as alkan	15
15	Examples of the base used in the case alkali acetates; dertiary	
	hydroxides, alkali hydrogencarbonates, alkali carbonates, or alkali acetates; tertiary	
	amines such as trimethylamine, triethylamine, tributylamine, pyridine, N-methylpiper-	
	It was the second continue and continue; and secondary annies such as at	
		-
	the feet and an east in the process (A), the reaction of the process (B) may be	20
20		
•	effected in the presente of a dehydrating carbodijimide. N.N'-diethyl carbodi-	
	effected in the presence of a denydrating contesting again, and a carbodi- carbodiimide, N-cyclohexyl-N'-morpholinoethyl carbodiimide, N,N'-diethyl carbodi- carbodiimide, N-cyclohexyl-N'-morpholinoethyl carbodiimide, N,N'-diethyl carbodi-	
•		
	c 1	25
25	4 4 4 1:	23
23	1,3,2-dioxaphospholane of Gazzolyi charlet metal salts, ammonium salts, and salts with includes alkali metal salts, alkaline earth metal salts, ammonium salts, and salts with	
	organic bases such as trimethylamine or dicyclohexylamine.	
	When B in the formula (VI) is a group other than a hetero aromatic N-oxide thio	*
	When B in the formula (VI) is a group other than a the Novide group in the	30
30		50
50		
		-
	dimethoxyethane, dimethylformamide, dimethyl sulfoxide, dichloromethane, chloro-	35
35	dimethoxyethane, dimethylormalinde, dimethylormalin	
	to the major columns are to the territory in this case. The Dri di the leaching solution to	
	and the addition of a buffer colution such as socialin diabolitate. The leaction con	
	This are not noticularly limited though the reaction is ordinarily conducted at o	40
40	46666	
	aromatic N-oxide this group having a this group on the carbon atom adjacent to the	
	aromatic N-oxide tino group having a tino group of formula (VI) is reacted with the	
	N-oxide group in the molecule, the compound of formula (VI) is reacted with the	
•		45
45	- 1 This section to northwestern which all alcolled to door occur as the section of	43
45	-1Lal sebest alcohol meanti alcohol isonificity alcohol decolor, compared alcohol decolor, compared alcohol meanti-	
	the state of the ground the second the secon	
	ceeds smoothly by using an execution of this process includes organic and inorganic	
		50
50	ones, such as cupric chloride, bromide, fluoride, nitrate, sulfate, borate, phosphate,	
•	-11- f acotate propionate clitale, lalafale, Delizuale and Sanejiate. The	
		_
	formula (VII), though they are usually selected from the range of 0° to 100°C and	55
55	formula (VII), though they are usually segrectively	
	the range of several minutes to several days, respectively.	
	The reaction conditions to be adopted in the processes (1), (2) and (3) are not	
	limited to those mentioned above, and can be properly varied depending upon the kinds	•
	A construction of the contract	60
	The star also man toxic calts of the general formula (1), ill winch is a said	60
60	A 1 III III III III AMANIN AMANINA ACCORDING TO SID ARTHURLY DIUCCUUL MUM COM	
	1 Cata association (1) in which K- is a number atom of a discums broads	
	pounds of the general formula (1), in which (1) of the present invention, the penicillins Thus, among the compounds of formula (1) of the present invention, the penicillins	
•	Thus, among the compounds of the afforcasid processes (1) and (2) while	
	can be easily obtained according to any of the aforesaid processes (1) and (2), while	
		-

3 X		
	the cephalosporins can be easily obtained according to either the aforesaid process (1), (2) or (3).	•
5	The present penicillins and cephalosporins include concretely the following compounds though are not restricted thereto. The following penicillins can be produced by any of the aforesaid processes (1) and (2), and the following cephalosporins can be produced by any of the aforesaid processes (1), (2) and (3).	_ 5
•	Penicillins: $6 - [D(-) - \alpha - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacet-$	
40	amidol penicillanic acid.	10
10	$6 - [D(-) - \alpha - (4 - dichloroacetyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid,$	10
	6 - [D(-) - α - (4 - enanthoyl - 2 - oxo - 1 - piperazinocarbonylamino)phenyl- acetamido]penicillanic acid,	
15	$6 - [D(-) - \alpha - (4 - \text{cyclohexanecarbonyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonyl-amino})$ phenylacetamido] penicillanic acid,	15
	$6 - [D(-) - \alpha - (4 - acetyl - 3 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid,$	•
	$6 - [D(-) - \alpha - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid,$	
20	$6 - [D(-) - \alpha - (4 - n - hexyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	20
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
er 06	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 6 - methyl - 2 - oxo - 1 - piperazinocarbonyl-$	25
. 25	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - octyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	23
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - pivaloyloxymethyl - 2 - oxo - 1 - piperazinocarbonylamino)-$	
30	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - palmitoyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	30
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - capryloyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - caproyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
35	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{chloroacetyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenyl-	.35
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - benzoyl - 2 - oxo - 1 - piperazinocarbonylamino) phenyl-$	•
40	ida]nonicillania acid	40
.0	6 - $[D(-) - \alpha - (4 - p - chlorobenzoyl - 2 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,$	
	phenylacetamido] penicinanic acid, $6 - [D(-) - \alpha - (4 - p - methoxybenzoyl - 2 - oxo - 1 - piperazinocarbonyl- amino)phenylacetamido] penicillanic acid,$	
45	$6 - \{D(-) - \alpha - [4 - (3,4,5 - \text{trimethoxybenZoyl}) - 2 - 0x0 - 1 - \text{piperazino}\}$	45
	$6 - \{D(-) - \alpha - [4 - (2,4 - \text{dichlorobenzoyl}) - 2 - 0x0 - 1 - \text{piperazmocarounyl-} $	
50	6- [D(-) - α - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-	50
50	6 - [D(-) - α - (4 - phenylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl	30
3	6-[D(-) - α - (4 - ethoxycarbonyl - 2 - oxo - 1 - piperazinocarbonylamino)	
<u>.</u> 55	$6 - [D(-) - \alpha - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino) pitenylacet$	55
	amido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	
60	amido] penicillanic acid, $6 - [D(-) - \alpha - (4 - isopropyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	60
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - pentyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido] penicillanic acid,	

34		
	$6 - [D(-) - \alpha - (4 - iso - pentyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
	$6 - [D(-) - \alpha - (2 - \text{methyl} - 4 - n - \text{butyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonyl}$. 1
5	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 5 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	5
	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	=
	amino)phenylacetamido]penicillanic acid, 6 - [D() - α - (4 - benzyl - 3 - οχο - 1 - piperazinocarbonylamino)phenylacet-	
10	amido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \beta - \text{hydroxyethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$	10
-	shonylocatamidal nenicillanic acid	
	bhenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - acetyl - 2 - methyl - 3 - oxo - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,$	15
15	6 - [D(-) - α - (4 - carbamoyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonyl-	15
	$6 - [D(-) - \alpha - (3 - oxo - 1 - piperazinocarbonylamino) phenylacetamico) peni-$	
	cillanic acid, $6 - [D(-) - \alpha - (2,5 - dimethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-$	20
20	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (5 - \text{methyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	-,-
	amido] penicilanic acid, $6 - [D(-) - \alpha - (2 - ethoxycarbonylmethyl - 3 - oxo - 1 - piperazinocarbonyl-$	
25	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacet-$	25
25	amidal nanicillanic acid	
	anindo] penicinanic acid, $6 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ propionamido] penicillanic acid,	
30	6 - [D(-) - α - (4 - allyl - 3 - oxo - 1 - piperazinocarbonylamino) pnenylacet-	30
50	$6 - [D(-) - \alpha - (4 - \alpha - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)$	
	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \beta - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino) -$	
35	phenylacetamido] penicillanic acid, $6 - \{D(-) - \alpha - [4 - (trans - 2 - butenyl) - 3 - oxo - 1 - piperazinocarbonyl-$	35
•	amino] phenylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - n - heptyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
40	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - octyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	40
	acetamida I nenicillanic acid.	
	$6 - [D(-) - \alpha - (4 - n - dodecyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	4È
45	$6 - [\tilde{D}(-) - \omega - (4 - \text{cyclopentyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$	45
	$6 - [\hat{\mathbf{D}}(-) - \alpha - (4 - \text{phenylaminocarbonyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonyl-amino})$ phenylacetamido] penicillanic acid,	
	$6 - [D(-) - \alpha - (2 - phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-$	50
50	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	-
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - benzoyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	55
55	acetamida Inenicillanic acid.	
	$6 - [D(-) - \alpha - (4 - methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid,$	
60	$6 - [\hat{D}(-) - \alpha - (4 - \text{benzyl} - 2,5 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	60
	$6 - [\tilde{D}(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	
	$6 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) pnenyl-$	
	acetamido] penicillanic acid,	

33	1,508,062	33
	6 - $[D(-)$ - α - $(4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamido] penicillanic acid, 6 - $[D(-) \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	
j E	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	5
5	phenylacetamido] penicillanic acid, 6 - $[D(-)$ - α - (4 - acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	
•	phenylacetamido] penicillanic acid, 6 - [D(-) - α - (4 - allyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-	
10	acetamido I penicillanic acid.	10
	$6 - [D(-) - \alpha - (4 - phenyl - 2, 3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid,$	
	$6 - [D(-) - \alpha - (4 - \beta - \text{chloroethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] penicillanic acid,	
15	$6 - [D(-) - \alpha - (6 - methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	15
	amino) phenylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	
	phenylacetamido penicillanic acid, $6 - [D(-) - \alpha - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
20	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	20
		-
	phenylacetamido penicillanic acid, $6 - [D(-) - \alpha - (4 - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,$	25
25	6 - [D(-)] - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)	25
	$6 - ID(-) - \alpha - (4 - \text{ethyl} - 2.3 - \text{dioxo} - 1 - \text{piperazinothiocarbonylamino})$	ii
	phenylacetamido] penicillànic acid, $6 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-$	30
30	hydroxyphenylacetamido]penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p$	30
	hydroxyphenylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-$	
	cyclohexadienylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - 1,4-$. 35
35		
•	6 - [D(-) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)- 1,4 - cyclohexadienylacetamido [penicillanic acid,	
40	$6 - [D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-cyclohexadienylacetamido] penicillanic acid,$	40
40	6 - [DL - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2- thienylacetamido] penicillanic acid,	
	$6 - [DL - \alpha - (4 - ethyl - 2, 3 - dioxo - 1 - piperazinocarbonylamino) - 2 - thienyl-$	
45	acetamido] penicillanic acid, $0 - [DL - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - properadinocarbonylamino) - 2-$	45
	thienylacetamido] penicillanic acid, 6 - [DL - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-	
	thienylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazinocarbonyl-$	
50	amino \nhenvlacetamido nenicillanic acid.	50
	$6 - [D(-) - \alpha - (3,5 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}]$ - penicillanic acid,	*
-	$6 - [D(-) - \alpha - (2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	
. 55	$6 - [D(-) - \alpha - (4 - benzyl - 2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanic acid,$	55
	$6 - [D(-)] - \alpha - (4 - B, B, B) - trichloroethoxycarbonyl - 2,2 - pentamethylene - 3,3 -$	
	dioxo - 1 - piperazinocarbonylamino) phenylacetamido] penicillanic acid, 6 - $[D(-)$ - α - $(4$ - benzyl - 2 - methyl - 2 - phenyl - 3 , 5 - dioxo - 1 - piper-	60
60	azinocarbonylamino) phenylacetamido] penicillanic acid, pivaloyloxymethyl 6 - $[D(-)$ - α - $(2$ - methyl - 3 - 0 x0 - 1 - piperazino-	UU
	carbonylamino) phenylacetamido] penicillanate, phthalidyl 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	
	amino)phenylacetamido]penicillanate,	65
65	· · · · · · · · · · · · · · · · · · ·	

34	1,00,002	
	phthalidyl 6 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl-	
•	amino) phenylacetamido) penicillanate, phthalidyl 6 - [D() - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazino-	·
	carbonylamino) phenylacetamido] penicillanate, phthalidyl 6 - $[D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	5 ື
5	amino) nhenviacetamido i nenicillanate.	J
	methoxymethyl 6 - $[D(-)]$ - α - $(4$ - methyl - 2,3 - dioxo - 1 - piperazinocar-	=
	bonylamino) phenylacetamido) penicillanate, methoxymethyl $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl} -$	40
10	amina) nhanylacetamidal nenicillanate.	10
	methoxymethyl 6 - $[D(-)$ - α - $(4 - n - butyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate,$	
•	methoxymethyl 6 - $[D(-)]$ - α - $(4$ - iso - propyl - 2,3 - dioxo - 1 - piperazino-	
	carbonylamino) phenylacetamido penicillanate, methoxymethyl 6 - $[D(-) - \alpha - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino-$	15
15	carbonylamino) nhenylacetamidol nenicillanate.	
	pivaloyloxymethyl 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido] penicillanate,$	
	pivalovloxymethyl 6 - $[D(-)]$ - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocar-	20
20	bonylamino) phenylacetamido] penicillanate, pivaloyloxymethyl 6 - $[D(-) - \alpha - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino-$	20
	carbonylamino) phenylacetamido] penicillanate.	•
:	β - piperidinoethyl 6 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate,	
25	β - piperidinoethyl 6 - $[D(-) - \alpha - (4 - n - octyl - 2, 3 - dioxo - 1 - piperazino-$	25
23	carbonylamino) phenylacetamido] penicillanate, β - morpholinoethyl 6 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazino-	
	carbonylamino) phenylacetamido] penicillanate and β - morpholinoethyl 6 - [D(-) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino-	
	β - morpholinoethyl 6 - $[D(-) - a - (4 - 11 - octyl - 2)]$ - dioxo - 1 - piperamino carbonylamino) phenylacetamido] penicillanate.	30
30		
•	Cephalosporins: $7 - [D(-) - \alpha - (4 - methyl - 2, 3 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	35
35		
	7 - [D(-) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)- phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,	
	$7 - (D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
40	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	40
40	phenylacetamidol $= 3$ = methyl $= A^3$ = cephem $= 4$ = carboxylic acid,	
	7 - $[D(-)$ - α - $(4 - n - \text{hexyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,	
	$7 - 1D(-1) - \alpha - (4 - n - heptyl - 2.3 - dioxo - 1 - piperazinocarbonylamino) -$. 45
45	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	45
	nhenvigcetamido] = 3 = methyl = A' = cenhem = 4 = carboxviic acid,	•
	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,	
50	$7 - (D(-) - \alpha - (4 - n - propyl - 2.3 - dioxo - 1 - piperazinocarbonylamino)-$	50
	phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	-
	acetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	
	phenylacetamidol = 3 = acetoxymethyl = Λ° = cenhem = 4 = carboxylic acid,	55-
55	7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)- phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,	
	$7 - (1)(-) - \alpha - (4 - methyl - 2.3 - dioxo - 1 - piperazinotniocarbonylamino)-$	
	phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-	60
60	acetamido] $-3 - [2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl}) \text{thiomethyl}] - \Delta^2 - cephem -4$. 00
	carboxylic acid,	
	acetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4-	65
65	carboxylic acid,	•

53	1,500,002	-
	7 - $[D(-)$ - α - $(4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - \Delta^3-cephem - 4 - carboxylic acid,$	
5	$7 - [D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,$	5
ä ,	$7 - [D(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)pnenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl)thiomethyl] - \Delta^3 - cephem - 4-$	10
10	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ pnenytacetamido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl})$ thiomethyl] - Δ^3 - cephem - 4-	10
15	carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 6 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl- amino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]- Δ^3 - cephem - 4 - carboxylic acid,	15
-	7 - $[D(-)$ - α - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - $[5$ - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 -	~
20	7 - $[D(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)pinenyl-acetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - \Delta^3 - cephem - 4-$	20
	$7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocaroonylamino/pinenyl-acetamido}] - 3 - [5 - (1,3,4 - \text{thiadiazolyl}) thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	25
25	7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) piletyl- acetamido] - 3 - [5 - (1,3,4 - thiadiazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic	
30	$7 - [D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ acetamido] $-3 - [2 - (1 - \text{methyl} - 1, 3, 4 - \text{triazolyl})$ thiomethyl] $-\Delta^3$ - cephem -4 -carboxylic acid.	30
	acetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid, 7 - [D(-) - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	35
35	acetamido] - 3 - [2 - (1 - metnyl - 1,5,4 - triazoly) thiometry $f = 2$ - cephen carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) propion-	•
40	amido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p- hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]-	40
	Δ^3 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl- acetamido] - 3 - azidomethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	45
45	acetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	43
50	acetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4-carboxylic acid, 7 - [D() - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic	50
, 	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl)thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	55
. 55 	acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic	
60	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - oxadiazolyl)thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,$	60
65	7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[3$ - (2,6 - dimethyl - 5 - oxo - 2,5 - dihydro - 1,2,4 - triazinyl)thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	65

36	1,508,062	
	acetamido] - 3 - [2 - (4 - methyloxazolyl) - thiomethyl] - Δ^{g} - cephem - 4 - carboxylic	
	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino]phenylacetamido] - 3 - [2 - (4 - methylthiazolyl)thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	5 ⁻
5	acid, $7 - [D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) phenylacetamido] - 3 - [2 - (pyridyl - 1 - oxide) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	Ä.
10	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - (2 - thiazolinylthiomethyl) - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [2 - (1 - methylimidazolyl)thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	10
15	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - (2 - pyrimidinylthiomethyl) - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [3 - (6 - methylpyridazinyl)thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	15
20	acid, 7 - [D(-) - α - (4 - methyl - 2,3 - díoxo - 1 - piperazinocarbonylamino)phenyl- acetamido] - 3 - [1 - (4 - methylpiperazino)thiocarbonylthiomethyl] - Δ^3 - cephem- 4 - carboxylic acid,	20
	$7 - [D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ acetamido] $-3 - [5 - (3 - \text{methylisoxazolyl})$ carbonylthiomethyl] $-\Delta^3$ - cephem -4	-
25	7- $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ acetamido] - 3 - ethoxythiocarbonylthiomethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{ethoxycarbonyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$	25
30	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)]$ - α - $(4 - n - \text{hexyl}]$ - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)]$ - α - $(4 - \text{acetyl}]$ - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2 - (5 - \text{methyl}]$ - $1,3,4$ - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-	30
35	carboxylic acid, $7 - [D(-) - \alpha - (4 - \text{methanesulfonyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) - \text{phenylacetamido}] - 3 - [2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl}) - \text{thiomethyl}] - \Delta^3- cephem - 4 - carboxylic acid, \frac{1}{2} - \frac{1}{2}$	35
40	acetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ° - cephem-4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ° - cephem - 4-	40
45	carboxylic acid, $7 - [D(-) - \alpha - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-amino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem-$	45
50	4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid, 7 - [D(-) - α - (3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]-	50
55	3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-	.55
60	4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)$ phenylacet- amido] - 3 - $[5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4-$	60
OU	carboxylic acid, 7 - [D(-) - α - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)- phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-	

	amido] - 3 - $[5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,$	
	7 - $[D(-)$ - α - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-	
	7 - [D(-) - a - (4 - ciny) - 2 - 000 - 1 - piperazinotanto obylanino)pinchylacter	
÷ _	amido] $-3 - [5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid,$	5
5	7 - $[D(-)$ - α - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-	•
•	amino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]-	
	Δ ³ - cephem - 4 - carboxylic acid,	
10	7- $[D(-)$ - α - $(4$ - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacet-	10
10	amido] $-3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4-$	10
٠.	carboxylic acid,	
	7 - $[D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	
	amido] - 3 - $[5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^8 - cephem - 4-$	
	carboxylic acid,	15
15	$7 - [D(-) - \alpha - (3.5 - \text{diox} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}]$	13
	$3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	
	acid,	
	7 - $[D(-)$ - α - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-	
••	acetamido] - 3 - [D - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-	20
20	4 - carboxylic acid, and	20
	methoxymethyl 7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-$	
	carbonylamino)phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylate.	
	The susceptible test of typical compounds among the compounds of the present	
	invention are shown below.	25
25	(1) The minimum inhibitory concentrations (MIC) of the compounds against	23
	different standard strains are shown in Tables 3 and 4.	
	The minimum inhibitory concentration (MIC) was determined by the plate method	•
	disclosed in "Chemotherapy" (Japan), Vol. 16, (1968), pages 98-99. The culture	
	medium used was a Heart infusion agar (pH 7.4). The number of the cells per plate	30
30	used in the inoculum was 10° (10° cells/ml).	50

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Suphylo Escherichia arriginata presumoniae aureus 209p (1.57 < 1.57 > 200 50 50					Desidoscopas		Proteus
ium < 1.57	Compound	ınd	Staphylo- coccus aureus 209p	Escherichia coil NIHJ	rseugononas aeruginosa I.F.O.	Klehsiella pneumoniae	vulgaris 3027
11um < 1.57	Chconh Sch3	(Sodium Ampicillin)	< 1.57	< 1.57	> 200	50	> 200
dium ulbenicillin) 3.13 , 1.57 50 > 200 	CO- CHCONH T S CH3	(Sodium Carbenicillin)	< 1.57	< 1.57	. 20	> 200	< 1.57
< 1.57 < 1.57 25 12.5	CHCONH SCH3	(Sodium Sulbenicillin)	3.13	1.57	50	> 200 >	0.79
	CH3CON NCONHCHCONH KS CH3	13 13 JONa	< 1.57	< 1.57	25	12.5	3.13

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Table

2 C12CHCOM MCONHICHCOMH SCH3 3 (H)-CON MCONHICHCOMH SCH3 4 CH3CON MCONHICHCONH SCH3 5 (H)-CON MCONHICHCONH SCH3 5 (H)-CON MCONHICHCONH SCH3 6 (1.57 < 1.57 < 1.57 25 12.5 3.13 7.13 7.13 7.13 7.13 7.13 7.13 7.13							
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		C12CHCON NCONHCHCONH SCH3	< 1.57	< 1.57	50	12.5	6.25
CH ₃ CON MCONHCHCONH S CH ₃ CH ₃ CH ₃ CON MCONHCHCONH S CH ₃ CH ₃ SO ₂ N NCONHCHCONH S CH ₃ CH ₃ SO ₂ N NCONHCHCONH S CH ₃ CH ₃ SO ₂ N NCONHCHCONH S CH ₃ CH ₃ SO ₂ N S CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ CH ₃ SO ₂ N S CH ₃ CONHCHCHCONH S CH ₃ CH ₃ CH ₃ CONHCHCHCONH S CH ₃ CH ₃ CH ₃ CH ₃ CONHCHCHCONH S CH ₃ CH ₃ CH ₃ CH ₃ CONHCHCHCONH S CH ₃		(H)-con nconheheonh s CH3	< 1.57	< 1.57	100	3.13	3.13
CH ₂ SO ₂ N NCONHCHCONH S CH ₃ CH ₂ 2.5 12.5 12.5	4	CH ₃ CON MCONHCHCONH CH ₃ CH	< 1.57	< 1.57	. 52	12.5	3,13
	S.	CH ₃ SO ₂ N NCONHCHCONH	< 1.57	< 1.57	25		< 1.57

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Table 3 (Cont'd)

9	CH ₂ (CH ₂) ₃ CH ₂ CON NCONHCHCONH CH ₂ CH ₃ CH ₃ CH ₃ COON _B	3.13	5.13	50	6.25	6.25
7	O-com nconhcheonh recona	< 1.57	< 1.57	200	12.5	6.25
.00	C1-(C)-CON NCONHCHCONH T S CH3	< 1.57	< 1.57	001	6.25	3.13
6	CH3-O-CON NCONHCHCONH SCH3	< 1.57	3.13	700	3.13	3.13

Table 3 (Cont'd)

Table 3 (Cont'd)

14 GH ₃ (CH ₂) ₂ CH ₂ M MCONHGHCONH S CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₂ M CONHGHCONH S CH ₃ CH ₃ CH ₂ M CONHGHCONH S CH ₃ CH ₃ CH ₂ M CONHGHCONH S CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₂ M CONHGHCONH S CH ₃ C							
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	14	CH ₃ (CH ₂) ₂ CH ₂ N NCONHCHCONH SCH ₃ CH ₃	< 1.57	< 1.57	25	3.13	< 1.57
CH ₃ (CH ₂) ₆ CH ₂ M MCONHCHCONH	15	CH ₂ (CH ₂) ₂ CH ₂ N NCONHCHCONH T S CH ₃ CH ₃ CH ₃ CH ₃ CH ₃ COONa	> 1.57	5.13	50	6.25	6.25
СН3N NCONHÇHCONH — S СН3 О	16	CH ₂ (CH ₂) ₆ CH ₂ N NCONHÇHCONH	< 1.57	< 1.57	12.5	1.57	< 1.57
	17	CH ₂ N NCONHCHCONH S CH ₃ CH ₃	< 1.57	ج ج ۲۰۰۲	12.5	50	6.25

Cont'd)
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Table

18	CH ₂ (CH ₂) ₂ CH ₂ N NCONHCHCONH	< 1.57	< 1.57	12.5	25	3.13
19	CH ₂ CH ₂ NCONHCHCONH S CH ₃	< 1.57	< 1.57	12.5	20	3.13
50	(CH ₂) ₂ CH ³ (CH ₃) ₂ CH ³ (O) CH ₃ (O) CH ₃	3.13	< 1.57	12.5	25	3.13
21	(CH ₃) ₂ CHCH ₂ CH ₂ N NCONHCHCONH CH ₃ CH ₃	< 0.79	1.57	. 52	25	3.13

Table 3 (Cont'd)

22	CH ₂ (CH ₂) ₂ CH ₂ ^N NCONHCHCONH	< 1.57	< 1.57	20	12.5	6.25
23	CH2N NCONHCHCONH SCH2	< 1.57	< 1.57	25	6.25	3.13
. 24	HOCH2CH2N NCONHCHCONH T S CH3	3.13	< 1.57	50	20	52
25	CH2=CHCH2N NCONHÇHCONH S CH3	< 1.57	< 1.57	. 25	20	3.13

Table 3 (Cont'd)

						•
26	CH ₂ =CHCHN NCONHCHCONH SCH ₃ CH ₃ CH ₃ CH ₃ CH ₃ CH ₃	< 1.57	< 1.57	25	25	12.5
27	CH ₂ =CCH ₂ N CONHCHCONH SCH ₃ CH ₃ O CONB	< 1.57	< 1.57	25	25	3.13
28	CH ₂ CH O CHCHCONH S CH ₃ CH	< 1.57	< 1.57	25	25	3.13
29	CH ₂ (CH ₂) ₄ CH ₂ ^N NCONHCHCONH CH ₂ CH ₂ CH ₂	3.13	< 1.57	12.5	3.13	5.13

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CH ₃ (CH ₂)6CH ₂ N NCONHCHCONH TT CH ₃ (O) O COONA	< 1.57	< 1.57	25	6.25	3.13
CH ₂ (CH ₂) ₁₀ CH ₂ N CONHCHCONH S CH ₃	< 1.57	< 1.57	12.5	6.25	< 1.57
H-N NCONHCHCONH TO STORY CH3	< 1.57	< 1.57	12.5	12.5	6.25
O-NHCON NCONHCHCONH S CH3	< 1.57	< 1.57	50	6.25	3.13

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	O-con nconhoriconh schiz	1.57	3.13	00τ	50	20
35.	O-ch-2N NCONHCHCONH SCH3	1.57	6.25	100	25	25
36 0	CH ₂ CH ₂ N NCONHCHCONH S CH ₃ CH ₃	< 1.57	< 1.57	6.25	< 1.57	< 1.57
37 6	CH ₂ N NCONHCHCONE SCH ₂ CH ₂	< 1.57	< 1.57	6.25	6.25	< 1.57

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Table 3 (Cont'd)

				The second secon		-
38	CH ₂ CH ₂ CH ₂ N NCONHCHCONH T S CH ₃	0.4	< 0.1	6.25	3.13	0.4
39	CH ₂ (CH ₂) ₂ CH ₂ MCONHQHCONH	0.4	< 0.1	6.25	1.57	0.4
40	CH2) 2 CHN NCONHCHCONH S CH3	0.4	< 0.1	6.25	3.13	4.0
41	CH3COOCH2CH2N NCONHCHCONH SKCH3	< 1.57	< 1.57	25	6.25	< 1.57

Table 3 (Cont'd)

42	CH2=CHCH2N NCONHCHCONH SCH3	1.57	< 1.57	12.5	6.25	< 1.57
43	O O O O O O O O O O O O O O O O O O O	< 1.57	< 1.57	6.25	1.57	< 1.57
44	C1CH2CH2N NCONHCHCONH S CH3	< 1.57	< 1.57	6.25	< 1.57	< 1.57
45	CH ₂ (CH ₂) ₃ CH ₂ N NCONHCHCONH CS CH ₂ O O CH ₂ (CH ₂) ₃ CH ₂ N CONHCHCONH COON _B	0.79	< 0.1	12.5	0.79	0.4

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Table	

1						
	CH ₃ (CH ₂) ₄ CH ₂ N CONHCHCONH	0.2	< 0.1	6.25	4.0	4.0
	CH ₂ (CH ₂) 6CH ₂ M NCONHCHCONH CH ₃ CH ₂ CH ₃	< 1.57	< 1.57	6.25	<1.57	< 1.57
	CH ₃ N NCONHCHCONH S CH ₃ O O COONB	< 0.4	< 0.4	6.25	25	> 0.4
49	CH3N NCONHCHCONH TS CH3	4.0 >	0.79	12.5	12.5	1.57

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50 CH3N MONHOGLONH SCHOOL SCHO							
CH3(CH2)6CH2NLMCONHCHCONH CHCH2OCH3 O CH3NLMCONHCHCONH CHCNLM CONHCHCONH CHCNLMCONHCHCONH CHCNLMCONHCHCONH CHCNLMCONHCHCONH CHCNLMCONHCHCONH CHCNLMCONHCHCONH CHCNLMCONHCHCONH CHCNLMCONHCHCMCONHCHCONH CHCNLMCONHCHCONH CHCNLMCONHCHCONH	50	CH ₃ N NCONHCHCONH S CH ₃ CH ₃ CH ₃ COCH ₂ OCH ₃	< 0.79	< 0.79	6.25	6.25	< 0.79
CH3N NCONHCHCONH SCH2 CH3N NCONHCHCONH SCH2	51	CH ₂ (CH ₂) ₆ CH ₂ N NCONHCHCONH SCH ₃ O COOCH ₂ OCH ₃	< 0.4	< 0.4	12.5	. O 0.4	\ 4.0 \
0 0 0 СH ₃ N NCONHCHCONH	25	CH ₃ N MCONHCHCONH S CH ₃ CH ₃ CH ₃ CH ₃ COOCH COO	0.79	0.79		25	1.57
	53	CH ₂ N NCONHCHCONH SCH ₂ CH ₂	0.79	< 0.4	6.25	52	0.79

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54	CH ₂ (CH ₂) 6 CH ₂ N NCONHCHCONH S CH ₃ CH ₂	0.79	4.0	12.5	0.79	0.79
55	CH ₃ N NCONHÇHCONH S CH ₃ S CH ₃ CH ₂ N O	0.79	4.0	6.25	25	0.79
56	CH ₂ (CH ₂) 6 CH ₂ N NCONHCHCONH CH ₃ CH ₃ CH ₃ CH ₂ N COOCH ₂ CH ₂ N COOCH ₃ CH ₃ N COOCH	4.0 >	< 0.4	12.5	1.57	0.79
57	CH ₃ N NCONHCHCONH S CH ₃ CH ₃ N CONHCHCONH CH ₃ COONa	< 0.79	< 0.79	12.5	12.5	3.13

Table 3 (Cont'd)

58	CH ₃ N NCONHCHCONH S CH ₃ CH	< 1.57	< 1.57	12.5	25	3.13
59	HN NCONHÇHCONH SCH3	< 1.57	< 1.57	25	200	3.13

Sodium Carbenicillin and Sodium Sulbenicillin are regarded as preferable drugs at the level of this technical field, and hence are described for (Note)

reference.

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Proteus vulgaris 3027	< 1.57	< 1.57	1.57	3.13
Klebstella pneumoniae	001	7000	500	500
Pseudomonas aeruginosa I.F.O.	> 200	> 200	> 200	500
Escherichia coli NIH3	< 1.57	< 1.57	/51.57	> 5.13
Staphylo- coccus aureus 209p	< 1.57	< 1.57	< 1.57	< 1.57
Compound	H ₂ NCHCONH	S CH2CONH S CH2OCOCH3 (Sodium Cophalothin)	$N=N$ $ N-CH_2CONH - S - N-N$ $ N-N - CH_2CONH - S - N-N$ $ N-N - CH_2CONH - N-N$ $ N-N - N-N - $	Cephaloridine) < 1.57
Com- pound No.		(τ	ortno)	

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60 CH3N WCONHCHCKONH							
CH3CHCHCHCONH CONHCHCONH CONHCHCONH CH2CCCCH3 O O CH3M NCONHCHCONH CH2S L L L L L CH3M CH3M CCH3M CH3M CH3M CH3M CH3M CH3	9	CH3N NCONHCHCONH S CH2OCOCH3	0.79	< 0.1	25	3.13	3.13
CH3N NCONHCHCONH TS N N N N N CONHCHCONH TS N N N CONHCHCONH TS N N N CH2S N N CONHCHCONH TS N N CH2S N N N CH2S N N N CH2S N N N N N N N N N N N N N N N N N N N	61	CH3CH2N NCONHCHCONH S CH2OCOCH3	< 0.79	< 0.79	25	3.13	3.13
CH3N NCONHCHCONH	62	CH ₃ N NCONHÇHCONH T S N-N CH ₂ S S CH ₃ CH ₃		ť.0 >	. 0%	1.57	3.13
	63	CH ₂ N NCONHCHCONH S CH ₂ S N-N CH ₂ S CH ₂ S N-N CH ₂ S CH ₂ S CH ₃ S	< 0.79	< 0.79	25	< 0.79	1.57

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64	CH3N NCONHCHCONH CH2S N-N	0.79	< 0.1	25	1.57	3.13	
65	$\begin{array}{c} 0 & 0 \\ \text{CH}_{2}N & \text{NCONHCHCONH} & \begin{array}{c} S \\ \end{array} & \begin{array}{c} N - N \\ \end{array} & \begin{array}{c} N - N \\ \end{array} & \begin{array}{c} O \\ \end{array} & \begin{array}{c}$	3.13	0.79	25	3.13	3.13	•
99	CH ₃ CH ₂ N NCONHCHCONH T S CH ₂ S N N N N CH ₂ S N N N N CH ₂ S N N N N N N N N N N N N N N N N N N N	< 0.79	< 0.79	52	0.79	< 1.57	

Table 4 (Cont'd)

67	CH3CH2N NCSNHCHCONH S CH3CH2N NCSNHCHCONH CH2 COONB	6.25	< 0.79	100	3.13	12.5
89	CH ₃ N CONHCHCONH S CH ₂ N COO	1.57	. 0 >	12.5	< 0.79	1.57
69	CH ₂ CH ₂ N CONHCHCONH S N-N CH ₂	< 0.79	< 0.79	12.5		< 0.79

- cont'd

Table 4 (Cont'd)

07	CH ₂ CH ₂ N NCONHCHCONH S CH ₂ S (Q)	< 0.79	1.57	100	1.56	< 0.79
12	CH ₃ N NCONHCHCONH S CH ₂ S N T CH ₃	< 0.79	< 0.79	50	2.56	< 0.79

(Note) Sodium Cephalothin, Sodium Cephazolin and Cephaloridine are regarded as preferable drugs at the level of this technical field, and hence are set forth for reference.

(2) The minimum inhibitory concentrations (MIC) of the compounds against clinical isolates of bacteria are shown in Tables 5 and 6.

MIC was determined in the same manner as in the preceding paragraph (1).

Table 5-1

_	/			S	Staphylococcus aureus	reus					
ပ	Compound	MS 8619	MS 8588	MS 8713	MS 8596	MS 8684	F-1	F-2	F-3	F-4	P-5
1	Sodium Ampicillin	< 0.4	6.25	3.13	1.56	1.56	12.5	0.79		12.5	50
outro	Sodium Carbenicillin	62.0	6.25	6.25	6.25	6.25	6.25	3.13	3.13	12.5	> 200
00	Sodium Sulbenicillin	3.13	3.13	3.13	3.13	3.13	6.25	3.13	6.25	6.25	> 200
°	Compound No. 1	1.57	6.25	3.13	3.13	3.13	12.5	3.13		6.25	> 200
	13	0.79	3.13	3.13	3.13	3.13	12.5	1.57		6.25	200
	" 14	0.79	3.13	3.13	3.13	3.13	12.5	1.57		6.25	82
	" 16	< 0.4	3.13	3.13	3.13	3.13	6.25	0.79		6.25	.100
	30	< 0.4	1.57	1.57	1.57	1.57	3.13	0.79	0.79	3.13	901

Table 5-1 (Cont'd)

Compound No. 36	يو	62.0	3.13	6.25	3.13	3.13	12.5	3.13	1.57	6.25	> 200
i.	77	67.0	3:13	12.5	3.13	3.13	12.5	1.57	3.13	6.25	> 200
- E	88	0.79	3.13	6.25	3.13	3.13	6.25	1.57	0.79	6.25	> 200
=	65	0.79	1.57	3.13	1.57	3.13	6.25	1.57	1.57	6.25	> 200
. "	ę	0.79	3.13	12.5	3.13	3.13	6.25	3.13	62.0	6.25	> 200
-	45	0.79	3.13	6.25	3.13	3.13	6.25	1.57	1.57	6.25	> 200
=	46	< 0.4	1.57	6.25	3.13	1.57	6.25	1.57	0.79	6.25	> 200
=	47	< 0.4	3.13	6.25	3.13	3.13	6.25	1.57	1.57	12.5	> 200

Table 5-2

V	· /				Escherichia coli					
~	Compound	GN 3481	GN 3435	GN 3452	GN 3465	GN 3611	K-1	K-2	K-3	K-4
от	Sodium Ampicillin	6.25	3.13	6.25		> 200	6.25	6.25	> 200	12.5
aquoo	Sodium Carbenicillin	6.25	6.25	12.5	> 200	> 200	6.25	6.25 >200	> 200	12.5
	Sodium Sulbenicillin	12.5	6.25	12.5	> 200	> 200	6.25	12.5	> 200	6.25
١	Compound No. 1	12.5	6.25	12.5	200		6.25	25 .	> 200	12.5
	" 13	6.25	3.13	3.13	25	-	3.13	6.25	100	6.25
	" 14	6.25	6.25	6.25	50		3.13	12.5	200	6.25
	. 16	3.13	1.57	1.57	12.5	-	1.57	3.13	20	3.13
	" 30	25	12.5	25	50	> 200	12.5	25	>200	12.5

Table 5-2 (Cont'd)

_							
1.57	3.13	0.79	0.79	0.79	0.79	< 0.4	0.79
> 200	>200	>200	>200	>200	200	20	100
3.13 >200	6.25 >200	3.13 >200	1.57 >200	3.13 >200	1.57	61.0	1.57
3.13	12.5	3.13	1.57	1.57	0.79	0.79	1.57
> 200	> 200	> 200-	> 200	> 200	> 200	> 200	> 200
100	200	50	. 25	50	25	6.25	6.25
3.13	12.5	3.13	0.79	1.57	1.57	0.79	1.57
1.57	3.13	0.79	0.79	0.79	0.79	< 0.4	67.0
3.13	6.25	3.13	1.57	1.57	1.57	3.13	1.57
. 36.	37	38	39	40	45	46	47
Compound No. 36	=	=	Ξ		=	=	=

Table 5-3

·		_		·	•			r		
	GN 383	^ 200	20	20	20	20	20	52	12.5	50
	GN 244	> 200	50	50	25	50	50	12.5	52	20
	GN 163	> 200	50	50	. 25	25	25	12.5	12.5	25
	GN 2987	> 200	50	25.	. 52	12.5	12.5	3.13	12.5	12.5
поѕа	GN 2565	> 200	200	100	50.	50	50	12.5	90	50
Pseudomonas aeruginosa	1601 NO	> 200	100	92	52	25	25	12.5	12.5	25
Psei	GN 221	> 200	25	25	52	50	25	25	12.5	20
	GN 82	> 200	100	50	25	50	52	6.25	12.5	25
	GN 376	> 200	50	50	25	20	05 .	25	12.5	05
	GN 1035	> 200	> 200	100	100	50	50	. 25	100	. 50
		ıllin	odium Carbenicillin	Sodium Sulbenicillin	No. 1	13	14	16	19	30
	Compound	Sodium Ampicillin	<i>(</i> / ₂		Compound No.	Ε	Ξ	=	=	=
<u> </u>		Ţ	ontro	ວ				1		

6.25	25	6.25	6.25	6.25	25	25	50
12.5	50	6.25	6.25	6.25	25	12.5	25
6.25	12.5	3.13	3.13	6.25	12.5	6.25	12.5
12.5	25	6.25	3.13	3.13	12.5	6.25	12.5
25	.25	12.5	12.5	12.5	25	12.5	25
6.25	12.5	3.13	3.13	6.25	12.5	12.5	12.5
3.13	6.25	6.25	3.13	6.25	3.13	12.5	25
6.25	6.25	3.13	3.13	6.25	12.5	6.25	12.5
6.25	12.5	3.13	6.25	3.13	25	25	50
25	50	12.5	12.5	25	50	50	25
36 .	37	38	39	40	45	46	47.
Compound No. 36	2	=		E	:	£	=

Table 5-4

										
	CN 917	25	> 200	> 200	25	12.5	25	12.5	50	25
umoniae	GN 3850	50		> 200	25	6.25	12.5	3.13	100	52
Klebsiella pneumoniae	GN 4081	> 200	> 200	> 200	> 200	52	95	52	> 200	100
	GN 4117	> 200	> 200	> 200	200	25	50	25	> 200	100
	S-4	> 200	200	1.00	95	50	50	25	50	50
aernginosa	S-3	> 200	200	00τ ΄	20	100	100	50	. 50	. 100
Pseudomonas aernginosa	S-2	> 200	200	00τ	00τ	50	50	25	20	20
d .	S-1	> 200	200	00τ	50	50	. 50	12.5	50	20
/	Compound	Sodium Ampicillin	Sodium Carbenicillin	Sodium Sulbenicillin	Compound No. 1	13	" 14	. 16	. 19	. 30
/	တိ		toring	0 0	ပိ				<u> </u>	<u> </u>

cont'd -

Table 5-4 (Cont'd)

						,	,
6.25	12.5	3.13	1.57	6.25	1.57	0.79	1.57
12.5	25	6.25	3.13	12.5	3.13	1.57	3.13
100	200	50	25	100	25	12.5	12.5
100	100	50	25	50	25	3.51	12.5
50	001	12.5	12.5	12.5	25	20	20
25	. 05	12.5	52	25	20	05	95
12.5	52	12.5	5°21	52	25	20	05
50	200	12.5	12.5	12.5	. 25	50	50
No. 36	37	38	39.	40	45	. 46	47
Compound No.	ŧ	=	.	=	· e	=	=

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Table 5-5

	<u> </u>		г					
nella urium	SI 858	3.13	12.5	25	12.5	0.79	1.57	1.57
Salmonella typhi-murium	SL 2136	> 200	> 200	> 200	> 200	500	. 200	100
la typhi	ST 819	1.56	6.25	6.25	6.25	6.25	6.25	3.13
Salmonella typhi	SL 2169	0.78	3.13	1.57	6.25	3.13	3.13	1.57
Shigella flexneri	JS 11839	1.57	12.5	12.5	3.13	1.57	3.13	0.79
Shigella	JS 11215		> 200	> 200	001	12.5	52	6.25
Shigella sonnei	JS 11232	> 200	> 200	>200	> 200	12.5	52	6.25
Shigella	25LTT 81	67.9	12.5	> 200	12.5	3.13	6.25	1.57
	Compound	Sodium Ampicillin	Sodium Carbenicillin	Sodium Sulbenicillin	Compound No. 1	1.3	" 14	16
/	ŏ	τ	ontro	0	ပ			

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6.25	12.5	3.13	0.79	6.25	0.79	< 0.4	< 0.4 4.0 >
> 200	> 200	200	001	> 200	200	50	50
1.57	6.25	1.57	0.79	1.57	1.57	1.57	3.13
1.57	3.13	0.79	0.79	1.57	0.79	62.0	1.57
3.13	6.25	1.57	0.79	3.13	1.57	62.0	1.57
100.	> 200	25	25	. 50	. 25	6.25	6.25
50	100	50	25	50	25	12.5	6.25
3.13	6.25	3.13	1.57	3.13	1.57	0.79	. 0.79
No. 36	37	38	39	40	45	46	47
Compound No. 36	£	=	= .	=	=	=	z.

Table 5-6

			Proteus		
	Compound	mirabilis	morganii	vulgaris	rettgeri
T	Sodium Ampicillin	. < 1.57	< 1.57	< 1.5	200
outro	Sodium Carbenicillin	8.0	0.4	0.8	> 200
က် 	Sodium Sulbenicillin	62.0	< 0.4	< 0.4	> 200
<u> </u>	Compound No. 16	1.56	95°t	0.8	6.25
	. 30	3.13	3.13	3.13	12.5
<u> </u>	" 36	6.0	< 0.4	< 0.4	12.5
	37	62.0	0.79	<.0.4	25

cont'd -

Table 5-6 (Cont'd)

		10	<u></u>	2	6
12.5	6.25	6.25	6.25	3.13	0.79
< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4
< 0.4	< 0.4	0.79	0.79	< 0.4	4.0 >
< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4
No. 38	39	40	45	46	4.7
Compound No. 38	z	Ξ	=.	=	=

Table 6-1

<u>/</u>	-				Staphylococcus aureus	ureus					
ŏ	Compound	MS 8619	MS 8588	KI 8713	MS 8596	MS 8684	F-1	F-2	F-3	F-4	F-5
	Sodium Cephaloglycin	1.56	3.13	3.13	1.56	1.56	3.13	1.56	1.56	3.13	25
гьот	Sodium Cephalothin	< 0.4	< 0.4	< o.4	** 0 >	< 0.4	<0.4 <0.4	<0.4	<0.4	< 0.4	1.56
Con	Sodium Cephazolin	< 0.4	< 0.4	< 0.4	< 0.4	< o.4	0.78	0.78 < 0.4	<0.4	<0.4	0.78
	Cephalorizine	,< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	< 0.4	<0.4	<0.4	<0.4	0.78
ပ	Compound No. 60	0.78	1.56	0.78	0.78	1.56	3.13	82.0	1.56	1.56	.50
	" 61	95°T	1.56	1.56	- 1,56	1.56	3.13	95•τ	95°τ	3.13	50
	62	92.0	1.56	1.56	0.78	1.56	3.13	0.78	95°τ	1.56	12.5

Table 6-1 (Cont'd)

1	_ю Т	<u></u>
12.5	0.78	0.78
3.13 0.78 1.56 1.56 12.5	1.56 1.56 0.78 6.25	3.13
1.56	0.78	3.13 1.56 0.78
0.78	1.56	1.56
3.13	1.56	3.13
1.56	1.56	1.56
1.56	1.56	1.56
1.56	3.13	1.56
1.56	1.56	1.56
0.78	0.78	0.78
. 63	68	69
Compound No. 63	Ξ	æ

Table 6-2

	_				Escherichia coli	ii				
д 60 20	Compound	GN 3481	GN 3435	GN 3452	GN 3465	GN 3611	K-1	K-2	K-3	K-4
တ္ထိ	Sodium Cephaloglycin	3.13.	1.56	3.13	12.5	25	1.56	1.56	25	12.5
Lo _T trol	Sodium Cephalothin	12.5	6.25	12.5	52	50	6.25	6.25	100	. 25
l	Sodium Cephazolin	1.56	1.56	υ.56	6.25	25	1.56	1.56	> 200	3.13
_ ပ	Cephalorizine	3.13	3.13	3.13	. 05	100	3.13	3.13	200	6.25
Com	Compound No. 60	6.25	6.25	12.5	100	> 200	6.25	12.5	200	25
	. 61	3.13	3.13	6.25	50	200	3.13	6.25	100	6.25
	. 62	6.25	6.25	6.25	25	200	6.25	12.5	200	12.5
	63	3.13	3.13	12.5	25	00τ	3.13	6.25	50	6.25

	GN 244 GN 383	> 200 > 200	> 200 > 200	> 200 > 200	> 200 > 200	50 50	25 12.5	100 100
	GN 163	> 200	> 200	> 200	> 200	50	25	50
	GN 2987	> 200	> 200	> 200	> 200	95	. 25	50
osa	GN 2565	> 200	> 200	> 200	> 200	100	50	100
Pseudomonas aeruginosa	T60T N5	> 200	> 200	> 200	> 200	. 05	25	001
Pseuc	GN 221	> 200	> 200 -	> 200	> 200	12.5	6.25	50
	ĠN 82	> 200	> 200	> 200	> 200	50	25	. 100
	GN 376	> 200	> 200	> 200	> 200	90	12:5	, 100
	GN 1035	> 200	> 200	> 200	> 200	500	100	200
	Compound	Sodium Cephaloglycin	Sodium Cephalothin	Sodium C * Cephazolin	Cephalorizine	Compound No. 60	" 61	62.

Table 6-3 (Cont'd)

25	12.5	25
50	25	25
25	12.5	12.5
25	12.5	12.5
50	50	05
50	12.5	12.5
25	3.13	6.25
50	. 62.25	12.5
50	12.5	12.5
100	20	50
No. 63	89	69
Compound No. 63	2	r

Klebsiella pneumoniae	GN 4117 GN 4081 GN 917	3.13 3.13 1.56	6.25 12.5 3.13	3.13 3.13 1.56	12.5 12.5 3.13	25 25 6.25	12.5 12.5 6.25	25 12.5 6.25
	8-4	> 200	> 200	> 200	> 200	100	90	200
aeruginosa	S-3	> 200	> 200	> 200	> 200	001	50	200
Pseudomonas aeruginosa	S-2	> 200	> 200	> 200	> 200	100	50	300
	S-1	> 200	> 200	> 200	> 200	200	50	200
/	Compound	Sodium Cephaloglycin	Sodium Cephalothin	Sodium Cephazolin	Cephalorizine	Compound No. 60	61	62
<u>/</u>	ပ်		trol	uog		Ö	<u>L.</u>	

Table 6-4 (Cont'd)

		.,
3.13	1.56	0.78
6.25	1	1
6.25	•	•
100	25	50
700	25	50
100	52	25
100	25	25
No. 63	.89	69
Compound No. 63	£	z

Table 6-5

		Proteus		
Compound	ınirabilis	morganil	vulgaris	rettgeri
Sodium Cephaloglycin	3.13	1.56	50	50
Compound No. 60	3.13	3.13	1.56	6.25
. 61	1.56	1.56	0.8	3.13
. 62	6.25	3.13	3.13	6.25
. 69	3.13	3.13	1.56	3.13

(3) Resistant activity against β -lactamase, *Pseudomonas aeruginosa* GN 238: The resistant activity of each compound against β -lactamase was measured in the manner described below.

 β -Lactamase was prepared from Psuedomonas aeruginosa GN 238. This microorganism was cultured in 100 ml of a medium containing 2 g of yeast extract. 10 g of polypeptone, 2 g of glucose, 7 g of disodium hydrogen phosphate, 2 g of potassium dihydrogen phosphate, 1.2 g of ammonium sulfate and 0.4 g of magnesium sulfate, per liter, in a 500-ml Erlenmeyer flask for 6 hrs. at 37°C with shaking. The resulting cells were collected by centrifugation (5,000 r.p.m. × 10 min.), washed three times with 0.1 M phosphate buffer (pH 7.0). Subsequently, the cells were subjected to sonication (20 KH₂, 20 min.) and then centrifuged at 15,000 r.p.m. for 60 min. By using the supernatant of enzyme fluid, the resistance of each compound against β -lactamase was determined by the iodometric assay method. The results obtained were as set forth in Table 7. Each numeral shown in Table 7 is a relative activity value calculated by assuming as 100 the activity of the control Potassium Penicillin G.

Table 7

Comparison of resistant activity against β -lactamase

	Compound	Relative activity (%)
	Potassium Penicillin G	100
싷	Sodium Ampicillin	115
Control	Sodium Carbenicillin	116
ဦ	Sodium Sulbenicillin	50
0	Compound No. 30	3
	" 36	14
	" 37	15
	" 38	15
	" 39	15
	· n 40	15
	" 45	16
	" 46	12
	" 47	1

From Tables 3 to 6, it is understood that the compounds of the present invention have a broader antibacterial spectrum and more excellent antibacterial activity against not only *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Proteus* species but also many drug-resistant bacteria than the control ampicillin and cephaloglycin, i.e. compounds having an amino group at the α -position of the acyl group. It is also understood from Table 7 that the compounds of the present invention are far higher in resistance to β -lactamase than the control drugs.

·	As is clear from the above results, the compounds represented by the formula (Ie), among the compounds of the present invention, show prominent effects, and particularly preferable compounds are those of the formula (Ie), in which A represents a	
5	hydrogen atom, or an unsubstituted or substituted alkyl, alkenyl, aryl or aralkyl group; and R ² and R ³ represent individually a hydrogen atom or an alkyl group.	5
3	The present penicillins and cephalosporins have generally low toxicity. For example, $6 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ -phenylacetamido]penicillanic acid and $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{methyl})]$	\$
10	piperazinocarbonylamino)phenylacetamido]penicillanic acid have LD _{s0} (i.v. in mouse having a weight of 19±1 g) greater than 5 g/kg. The compounds of formula (I) of the present invention may be administered not	10
15	only in the form of free acids but also in the form of non-toxic salts or physiologically acceptable esters. Further, the compounds, which are in the form of physiologically unacceptable esters, are ordinarily put into uses after bringing them to the form of free acids or non-toxic salts by removing the ester-forming group according to a conventional procedure known in this technical field. The compounds of the present invention can be administered to humans and	15
20	animals after formulating them into a physiological form such as tablet, capsule, syrup, injection or the like which is usually adopted in the case of penicillin and cephalosporin type drugs.	20
	Procedures for producing the compounds of the present invention are shown below with reference to examples.	
25	Example 1. (1) To a mixture comprising 2.5 g of 1-acetyl-3-oxo-piperazine, 3.45 g of triethylamine and 20 ml of anhydrous dioxane was added a solution of 3.71 g of trimethyl-chlorosilane in 10 ml of anhydrous dioxane. The resulting mixture was refluxed for 17	25 -
30	hours and cooled to deposit triethylamine hydrochloride, which was then removed by filtration. The filtrate was dropped at -40° to -30°C into a solution of 1.8 g of phosgene in 30 ml of anhydrous methylene chloride. After the dropping, the resulting mixture was elevated in temperature, and reacted at room temperature for 30 minutes. Subsequently, the excess phosgene and the solvent were removed by distillation under reduced pressure to obtain 3.5 g of pale brown, oily 4-acetyl-2-oxo-1-piperazino-carbonyl chloride.	30
	IR (film) cm ⁻¹ : ν ₀₌₀ 1790, 1710, 1640	
35	(2) A suspension of 1.0 g. of $6-[D(-)-\alpha$ -aminophenylacetamido] penicillanic acid in 20 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension was dropped a solution of 900 mg of the afore-	35
40	said 4-acetyl-2-oxo-1-piperazinocarbonyl chloride in 5 ml of tetrahydrofuran at said temperature over a period of 30 minutes. During this period, the pH of the suspension was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the temperature of resulting mixture was elevated to 5° to 10°C, and the mixture was	40
45	reacted at said temperature for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by reduced pressure distillation, and the residue was dissolved in a mixed solvent comprising 30 ml of ethyl acetate and 10 ml of water. The resulting solution was adjusted to a pH of 1.5 to 2 by addition of dilute hydrochloric acid with ice-cooling, and then	45
50	the organic layer was separated off. The aqueous layer was re-extracted with 20 ml of ethyl acetate, and the resulting organic layer was combined with the aforesaid organic layer. The combined organic layer was washed with water, dried over anhydrous mag-	50 -
	nesium sulfate, and then ice-cooled. Into this organic layer was dropped a solution of 470 mg of a sodium salt of 2-ethylhexanoic acid in 20 ml of ethyl acetate to deposit white crystals. The deposited crystals were collected by filtration, washed with ethyl acetate and then dried to obtain 1.4 g of a sodium salt of $6-[D(-)-\alpha-(4-acetyl-2-oxo-$	÷
55	1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 205°C (decomp.), yield 94%.	55
	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1760 (lactam), 1600—1700 (—COO©, —CON<) NMR: [(CD ₈) ₂ SO+D ₂ O] τ values: 2.73 (5H), 4.35 (1H), 4.75 (2H), 5.75 (1H), 5.84 (2H), 6.42 (4H), 8.03 (3H), 8.52 (3H), 8.64 (3H)	
60	The above-mentioned operation was repeated, except that the 4-acetyl-2-oxo-1-	60

piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 8, to obtain the respective objective compounds as shown in Table 8. The structure of each objective compound was confirmed by IR and NMR.

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Table 8

Cl ₂ CHCO-N N-COCl	D(-)- C12CHCO-N N-CONHCHCONH SCH3 C12CHCO-N N-CONHCHCONH SCH3 M.P. (decomp.) 203 - 205°C, yield 73 % D(-)- CH3(CH2)4CH2CO-N N-CONHCHCONH SCH3 CH3(CH2)4CH2CO-N N-CONHCHCONH SCH3
(H)-co-N N-coc1	m.p. (decomp.) 202°C, yield 85.5 % D(-)- (H)-CO-N N-CONHCHCONH SCH3 (A)-CO-N N-CONHCHCONH COONA m.p. (decomp.) 203 - 205°C, yield 87.7 %

Table 8 (Cont'd)

chz o cocl	D(-)-CH ₂ O CH ₃ CO-N N-CONHCHCONH S CH ₃ (O) 0 COONa m.p. (decomp.) 199 - 200°C, yield 95 %
CH3SO2-N N-COC1	D(-)- CH ₃ SO ₂ -N N-CONHCHCONH SCH ₃ CH ₃ SO ₂ -N N-CONHCHCONH O O M.p. (decomp.) 199 ^o C, yield 80 %
сн ₂ (сн ₂) 4 сн ₂ -м м-сосл	D(-)- $CH_3(CH_2)_4CH_2-N$ O O O O O O O

Table 8 (Cont'd)

сн ₃ (сн ₂) ₂ сн ₂ -и м-сос1	D(-)- CH3(CH2)2CH2-N N-CONHCHCONH SCH3 CH3 CH2 O 0 COONB m.p. (decomp.) 158 - 161°C, yield 69 %
сн ₃ (сн ₂) ₂ сн ₂ -м м-сост	D(-)- CH ₃ (CH ₂) ₂ CH ₂ -N N-CONHOHCONH SCH ₃ CH ₃ O CH ₃ CH ₃ O O COONB m.p. (decomp.) 188 - 190°C, yield 81 %
сн ₃ (сн ₂) 6 сн ₂ -м м-сос1	D(-)- CH3(CH2)6CH2-N N-CONHCHCONH SCH3 CH3 O O O O O O O O O O O O O O O O O O O

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Table 8 (Cont'd)

D(-)-(CH₃)₃CCOOCH₂-N(N-COC1 (CH₃))

 $\begin{array}{c} D(-)- \\ (GH_{2})_{3}CCOOCH_{2}-N \\ \hline \\ m.p. (decomp.) 218^{O}C, yield 80 \% \end{array}$

Example 2.

acid in 30 ml of terrahydrofuran containing 20% by volume of water which had been cooled to 0°C, a solution of 2.5 g of 4-acetyl-2-oxo-1-piperazinocarbomyl chloride in 5 ml of terrahydrofuran was dropped at said temperature over a period of 30 minutes. During this period, the pH of the reaction solution was maintained at 1.0 to 12.0 by gradual addition of a 10% aqueous sodium hydroxide solution. Subsequently, the temperature of the resulting mixed solution was elevated to 5° to 10°C, and the solution was reacted at room temperature for 2 hours while maintaining the pH thereof at 10.0 to 11.0 by addition of a 10% aqueous sodium hydroxide solution. After the reaction, the tetrahydrofuran was removed by reduced pressure distillation. The residue was dissolved in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.0 to 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, washed with water and then dried over anhydrous magnesium sulfate. To this organic layer, a solution of 1.66 g of a sodium salt of 2-ethylhexanoic acid in 20 ml of ethyl acetate was added to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with ethyl acetate and then dried to obtain 1.89 g of a sodium salt of D(-)-c-(4-acetyl-2-oxo-1-piperazinocarbonylamino)phenylacetic acid, m.p. 115°C (decomp.), wield 50%.

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IR (KBr) cm⁻¹: vo. o 1690, 1650—1600

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(2) To a suspension in 15 ml of anhydrous acetone of 833 mg of the above-mentioned sodium salt of D(-)-a-(4-acetyl-2-oxo-1-piperazinocarbonylamino)phenylacetic acid was added 10 mg of N-methylmorpholine. The resulting mixture was colled to -20° to -15°C, and a solution of 286 mg of ethyl chlorocarbonate in 5 ml of anhydrous acetone was dropped into said mixture over a period of 5 minutes. Sub-

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sequently, the mixture was stirred at said temperature for 60 minutes. Into the thus treated mixture, a solution of 646 mg of a triethylamine salt of 6-aminopenicillanic acid in 30 ml of anhydrous methylene chloride was dropped at -40° to -30° C over a period of 10 minutes. Thereafter, the mixture was reacted with stirring at -30° to -20° C for 60 minutes, at -20° to -10° C for 30 minutes, and at -10° to 0° C for 30 minutes. After the reaction, the organic solvent was removed by reduced pressure distillation. The residue was dissolved in a mixed solvent comprising 50 ml of ethyl acetate and 20 ml of water, and the resulting solution was adjusted to a pH of 1.5 to 2.0 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, sufficiently washed with water and then dried over anhydrous magnesium sulfate, and the ethyl acetate was removed by reduced pressure distillation. The residue was dissolved in 50 ml of acetone, and the resulting solution was mixed with a solution of 340 mg of a sodium salt of 2-ethylhexanoic acid in 20 ml of acetone with ice-cooling to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with acetone and then dried to obtain 1.16 g of a sodium salt of $6 - [D(-) - \alpha - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino) phenylacetamido] penicillanic acid, m.p. 205°C (decomp.), yield 94%.$

Example 3.

(1) To a mixture comprising 1.0 g of 1-palmitoyl-3-oxo-piperazine, 0.6 g of triethylamine and 20 ml of anhydrous dioxane was added a solution of 0.65 g of trimethylchlorosilane in 10 ml of anhydrous dioxane. The resulting mixture was refluxed for 16 hours and cooled to deposit triethylamine hydrochloride, which was then removed by filtration. The filtrate was dropped at -40° to -30° C into a solution of 0.6 g of phosgene in 30 ml of anhydrous methylene chloride. After the dropping, the temperature of the resulting mixture was elevated and the mixture was reacted at room temperature for 30 minutes. Subsequently, the excess phosgene and the solvent were removed by reduced pressure distillation to obtain 1.1 g of pale yellow, oily 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride.

IR (film) cm⁻¹: $\nu_{C=0}$ 1740, 1660, 1640

(2) A suspension of 1.0 g of 6-[D(-)- α -aminophenylacetamido] penicillanic acid in 20 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension, a solution of 1.27 g of the aforesaid 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride in 5 ml of tetrahydrofuran was dropped at said temperature over a period of 30 minutes. During this period, the pH of the suspension was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the temperature of the resulting mixture was elevated to 5° to 10°C, and the mixture was reacted at said temperature for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by reduced pressure distillation, and the residue was dissolved in a mixed solvent comprising 30 ml of ethyl acetate and 10 ml of water. The resulting solution was adjusted to a pH of 1.0 to 2.0 by addition of dilute hydrochloric acid with ice-cooling, and then the organic layer was separated off. The aqueous layer was re-extracted with 20 ml of ethyl acetate, and the resulting organic layer was combined with the aforesaid organic layer. The combined organic layer was washed with water, and dried over anhydrous magnesium sulfate. This organic layer was concentrated under reduced pressure to remove the solvent, and the concentrate was charged into 10 ml of diisopropyl ether to deposit crystals. Thereafter, the crystals were collected by filtration to obtain 1.65 g of white crystals of $6-[D(-)-\alpha-(4-palmitoyl-2-oxo-1-piperazinocarbonylamino)$ phenylacetamido] penicillanic acid, m.p. 121—123°C (decomp.), yield 80%.

IR (KBr) cm⁻¹: $\nu_{C=0}$ 1770 (lactam), 1730 (—COOH), 1660—1630 (—CON<).

The above-mentioned operation was repeated, except that the 4-palmitoyl-2-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 9, to obtain respective objective compounds as shown in Table 9. The structure of each objective compound was confirmed by IR and NMR.

Table 9

Reactive derivative of compound of formula (III)	Objective compound
сн ₃ (сн ₂) ₅ сн ₂ со-м м-сос1	D(-)- CH ₃ (CH ₂) ₅ CH ₂ CO-N N-CONHCHCONH SCH ₃ (O) m.p. (decomp.) 151 - 153°C, yield 82 %
сн3(сн2)3сн2со-м м−сос1	D(-)- CH ₂ (CH ₂) ₃ CH ₂ CO-N N-CONHCHCONH SCH ₃ CH ₃ (CH ₂) ₃ CH ₂ CO-N N-CONHCHCONH CH ₂ COOH m.p. (decomp.) 157 - 158°C, yield 83.3 %
0 clcH2CO-N N-COCl	D(-)- C1CH2CO-N N-CONHCHCONH S CH3 C1CH2CO-N N-CONHCHCONH CH2 O 0 CH3 COOH M.p. (decomp.) 215°C, yield 82.6 %

Table 9 (Cont'd)

, (©)-co-w ⁰ ,-coc1	O-co-n n-conhchcone chi chi cooh o cooh n.p. (decomp.) 120 - 124°C, yield 80 %
c1-{O}-c0-N(N-c0c1	D(-)- C1-(O)-CO-N N-CONHCHCONH S CH3 (O) O 0 0.0. (decomp.) 120 - 123°C, yield 91 %
од СН3-{O}-со-и м-сос1	D(-)- CH3-(O)-CO-N N-CONHCHCONH SCH3 (O) O CH3-(CH3 (O) O CH3 (O) O CH3 (O) O CH3-(CH3 (O) O CH3 (O) O CH3-(CH3 (O) O CH3 (O) O CH3-(CH3 (O) O CH3 (O) O CH3 (O) O CH3-(CH3 (O) O CH3 (O) O CH3 (O) O CH3-(CH3 (O) O CH3 (O)

Table 9 (Cont'd)

сн ₃ 0 сн ₃ 0-со-и и-сос1 сн ₃ 0	D(-)- CH ₂ O D CH ₂ O CH CH ₂ O CH
c1 0 c1-C)-c0-N N-c0c1	D(-)- $_{G1}$ 0 $_{G1}$ C1- $_{G2}$ C1- $_{G3}$ C0- $_{N}$ C0- $_{C1}$ C0- $_{C1}$ C0- $_{C1}$ C00H $_{C1}$ C1- $_{C1$
CH3CONHCO-N N-COC1	D(-)- CH ₃ CONHCO-N N-CONHCHCONH S CH ₃ CH ₃ CONHCO-N N-CONHCHCONH CH ₃ O 0 m.p. (decomp.) 172 - 176°C, yield 79.2 %

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(Cont'd) Table 9

O NHCO-N N-COCI	D(-)- (O)-NHCO-N N-CONHCHCONH SCH3 (O)-NHCO-N N-CONHCHCONH CH3
	m.p. (decomp.) 168 - 170°C, yield 83.3 %
CH3CH20CO-N COC1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
	m.p. (decomp.) 86°C, yield 91 %

dimethylformamide was added 2.7 g of a sodium hydride (purity 53%) with ice-cooling and the resulting mixture was reacted at room temperature for 1 hour. Subsequently, the mixture was incorporated with 7.1 g of methyl iodide and reacted for 10 hours. After the reaction, the dimethylformamide was removed by reduced pressure distillation to obtain 1-formyl-4-methyl-3-oxo-piperazine. This piperazine was dissolved in 70 ml of a 50% aqueous acctone solution containing 2.2 g of sodium hydroxide, and the resulting solution was reacted at room temperature for 3 hours. Thereafter, the solvent was removed by distillation under reduced pressure, and the residue was charged into acctone to deposit insolubles. The insolubles were separated by illuration, and the methyl-2-oxo-piperazine, b.p. 104°C/4 mmHg, yield 91%.

(2) Into a solution of 1.9 g of phosgene in 20 ml of anhydrous dioxane was dropped at 10°C 20 ml of an anhydrous dioxane solution containing 2.0 g of 1-methyl-2-oxo-piperazine and 1.95 g of triethylamine, upon which reaction took place to deposit white crystals of triethylamine hydrochloride. The deposited crystals were removed by filtration, and the filtrate was concentrated to dryness to obtain 3.0 g of pale yellow, acetone was removed from the filtrate by distillation under reduced pressure. Subsequently, the residue was subjected to reduced pressure distillation to obtain 5.2 g of 1-ຊີ S 9 15

IR (film) cm⁻¹: 10=01710, 1630

oily 4-methyl-3-oxo-1-piperazinocarbonyl chloride.

5	(3) A suspension of 4.0 g of 6-[D(-)-α-aminophenylacetamido] penicillanic acid in 40 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension, 10 ml of a tetrahydrofuran containing 2.2 g of the aforesaid 4-methyl-3-oxo-1-piperazinocarbonyl chloride was dropped.	· 5
	During this period, the pH of the suspension was maintained at 7.5 to 8.5 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at said temperature for 30 minutes, and the temperature thereof was elevated to 10° to 15°C, after	3
10	which the mixture was further reacted at said temperature for 90 minutes while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 30 ml of water. The resulting solution was washed with ethyl acetate, and then the aqueous layer was separated off. This aqueous layer was ice-cooled and	10
_. 15	then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, washed several times with a small amount of water, dried, and then dissolved in 100 ml of acetone. To the resulting solution was added 1.9 g of a sodium salt of 2-ethylhexanoic acid with ice-cooling to deposit white crystals, which were then collected by filtration to obtain 5.4 g of a	15
20	sodium salt of 6- $[D(-)-\alpha$ -(4-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 195°C (decomp.), yield 92%.	20
	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1760 (lactam), 1600—1660 (—CON<, —COO ^{\ominus}) NMR [(CD ₃) ₂ SO+D ₂ O] τ values: 2.62 (5H), 4.48 (1H), 4.56 (2H), 5.97 (3H), 6.63—6.39 (4H), 7.13 (3H), 8.46 (3H), 8.55 (3H)	
25	The above-mentioned operation was repeated, except that the 4-methyl-3-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 10, to obtain respective objective compounds as shown in Table 10. The structure of each objective compound was confirmed by IR and NMR.	25

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Reactive derivative of compound of formula (III)	Objective compound
о сн ₃ (сн ₂) ₂ сн ₂ -и ју-сос1	$D(-) CH_3(CH_2)_2CH_2-N$ O
CH2CH2-N N-COC1	$CH_{2}CH_{2}-N$ $CH_{3}CH_{2}-N$ $CH_{3}CH_{2}-N$ $CH_{3}CH_{2}$ $CH_{3}CH_{2}$ $CH_{3}CH_{3}$
о (сн ₃) ₂ сн-и м-сос1	$D(-)- 0 CH_3)_2 CH-N N-CONHCHCONH CH_3 CH_3 CH_3 CONB O 0 0 0 COONB CO$

cont'd -

Table 10 (Cont'd)

сн ₃ (сн ₂) ₃ сн ₂ -м м-сос1	D(-)- $CH_{2}(CH_{2})_{3}CH_{2}-N$ $CH_{3}(CH_{2})_{3}CH_{2}-N$ $CH_{3}(CH_{2})_{3}CH_{2}-N$ $CH_{3}(CH_{2})_{3}CH_{2}-N$ CON_{3} CON_{3} CON_{3} CON_{4} COO_{6} COO_{6} COO_{6} COO_{6} COO_{6}
СН3)2СНСН2СН2-И У-СОС1	D(-)- (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH SCH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ CH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₃ (CH ₃) ₂ CHCH ₂ -N N-CONHCHCONH CH ₃ (CH ₃) ₂ CHCH ₃ (CH ₃) ₃ CHCH ₃ (CH ₃) ₄ CHCH ₄ (CH
осн ₃ (сн ₂) ₂ сн ₂ -и м-сос1	D(-)- CH ₃ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH SCH ₃ CH ₃ O O O O O O O O O O O O O O O O O O O

cont'd

Table 10 (Cont'd)

CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1 CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1 CH ₃ (CH ₂) ₂ CH ₂ -N N-COC1

cont'd

Table 10 (Cont'd)

HOCH2CH2-N-N-COC1	D(-)- HOCH2CH2-NN-CONHCHCONH SCH3 O O M.P. (decomp.) 100 - 105°C, yield 67 %
CH ₃ CO-N N-COC1	D(-)- O CH ₃ CH ₃ CO-N N-CONHCHCONH S CH ₃ (O O O O O O O O O O O O O O O O O O O
O CH ₃ H ₂ NCO-N N-COCL	$D(-)-0$ CH ₃ H_2NCO-N $N-CONHCHCONH$ $S \leftarrow CH_3$ O

cont. a

95

Table 10 (Cont'd)

O HW N-coc1	HN N-CONHCHCONH SCH3 COONE m.p. (decomp.) 213°C, yield 70 %
O CH ₃ HN N-COC1 CH ₃	D(-)- 0 CH3 HN N-CONHCHCONH S CH3 CH3 CH3 O CH3 m.p. (decomp.) 203 - 206°C, yield 82 %
0 HN N-6061 CH ₃	D(-)- O HN N-CONECHCONH CH ₂ CH ₂ CH ₃ CH ₂ CH ₃ CH ₂ Ch ₃ Ch ₄ Ch ₃ Ch ₄ Ch ₄ Ch ₄ Ch ₄ Ch ₅ Ch ₅ Ch ₅ Ch ₄ Ch ₄ Ch ₅ C

(Cont'd) Table 10

O CH2COOCH2CH3	D(-)- O CH2COOCH2CH3 HW N-CONHCHCONH CH3 O CH3 O CH2 O CH2 O CH2 O CH3 O CH2 O CH2 O CH3 O CH2 O CH3 O CH3 O CH3 O CH2 O CH2 O CH2 O CH3 O CH2 O CH3 O CH2 O CH3 O CH2 O CH2 O CH3 O CH2 O CH3 O CH2 O CH3 O CH2 O CH3 O CH2 O CH2 O CH3 O CH2 O CH2 O CH2 O CH3 O CH2 O CH2 O CH3 O CH2 O CH3 O
O CH ₃ HN N-COC1	D(-)- 0 CH ₂ HN N-CONHCHCONH S CH ₃ COONa O O CH ₃ O O CH ₃ O O CH ₃ O O O CH ₃ O O O O O O O O O O O O O O O O O O O

(1) A solution of 1.0 g of a sodium salt of D(-)-a-aminophenyl acetic acid in 20 ml of tetrahydrofuran containing 20% by volume of water was cooled to 0° to 5°C. To this solution was added 1.2 g of 2-methyl-3-oxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the solution was maintained at 11.0 to 12.0 by gradual addition of a 10% aqueous sodium hydroxide solution. The solution was reacted at said temperature for 1 hour, and the temperature thereof was elevated to 5° to 10°C, after which the mixture was further reacted at said temperature for 2 hours, while maintaining the pH thereof at 10.0 to 11.0 by addition of a 10% by distillation under reduced pressure, and the residue was dissolved in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate. The resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling, and then the organic layer was separated off. The aqueous layer was further extracted with 50 ml of ethyl acetate, and the resulting organic layer was combined with the aforesaid organic layer. The combined organic layer was washed with water and then dried over anhydrous magnesium sulfate. To this organic layer was added 0.9 g of a sodium salt aqueous sodium hydroxide solution. After the reaction, tetrahydrofuran was removed Example 5.

2

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	of 2-ethylhexanoic acid to deposit white crystals. The deposited crystals were collected by filtration and then dried to obtain 1.26 g of white crystals of a sodium salt of $D(-)$ - α - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetic acid, m.p. 215°C (decomp.), yield 70%.	
5	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1650—1590	5
-	(2) To a suspension in 15 ml of anhydrous acetone of 1.0 g of the above-mentioned sodium salt of $D(-)-\alpha$ -(2-methyl-3-oxo-1-piperazinocarbonylamino)phenylacetic acid was added 10 mg of N-methylmorpholine. The resulting mixture was cooled to -20° to -15° C, and a solution of 380 mg of ethyl chlorocarbonate in 5 ml of	J
10	annydrous acetone was dropped into said mixture over a period of 5 minutes. Subsequently, the mixture was stirred at said temperature for 60 minutes, and then cooled to -40° to -30°C. Into the thus treated mixture was dropped a solution of 960 mg of a triethylamine salt of 6-aminopenicillanic acid in 10 ml of anhydrous methylene chloride over a period of 10 minutes. Thereafter, the mixture was reacted with stirring at -30°	. 10
15	to -20° C for 60 minutes, at -20° to -10° C for 30 minutes, and at -10° to 0° C for 30 minutes. After the reaction, the organic solvent was removed by distillation under reduced pressure. The residue was dissolved in a mixed solvent comprising 20 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic	15
20	layer was separated off, sufficiently washed with water and then dried over anhydrous magnesium sulfate. To this organic layer was added 0.5 g of a sodium salt of 2-ethylhexanoic acid with ice-cooling to deposit white crystals. The deposited crystals were collected by filtration, and then dried to obtain 1.39 g of a sodium salt of $6-[D(-)-\alpha-(2-\text{methyl-3-oxo-1-piperazinocarbonylamino)})$ phenylacetamido] penicillanic acid, m.p.	20
- 25	208°C (decomp.), yield 90%. In the same manner as above, 2.0 g of a sodium salt of 6 - [D(-) - α-(4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)propionamido]penicillanic acid, m.p. 195°C (decomp.), yield 86%, was obtained from 1.59 g of a sodium salt of D(-) - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)propionic acid and	25
30	1.59 g of a triethylamine salt of 6-aminopenicillanic acid. IR (KBr) cm ⁻¹ : v ₀₌₀ 1760 (lactam), 1680—1600 (—CON<, —COO⊕)	30
	Example 6.	*
35	(1) Into a solution of 0.5 g of phosgene in 10 ml of anhydrous dioxane was dropped at 10°C 10 ml of anhydrous dioxane containing 0.56 g of 1-allyl-2-oxo-piperazine and 0.5 g of triethylamine, upon which reaction took place to deposit white crystals of triethylamine hydrochloride. Subsequently, the deposited crystals were collected by filtration, and the filtrate was concentrated to dryness to obtain 800 mg of pale yellow, oily 4-allyl-3-oxo-1-piperazinocarbonyl chloride.	35
	IR (film) cm ⁻¹ : $\nu_{0=0}$ 1720, 1640	
40	(2) A suspension of 1.4 g of $6-[D(-)-\alpha$ -aminophenylacetamido] penicillanic acid in tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring, and then cooled to 0°C. Into the thus treated suspension was dropped 10 ml of a tetrahydrofuran solution containing 800 mg of the aforesaid 4-allyl-3-oxo-1-piperazinocarbonyl chloride. During	40
45	this period, the pH of the suspension was maintained at 7.5 to 8.5 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at said temperature for 30 minutes, and the temperature thereof was then elevated to 10° to 15°C, after which the mixture was further reacted at said temperature for 90 minutes while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After the reaction, the	45
.50	tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water. The resulting solution was washed with ethyl acetate, and the aqueous layer was then separated off. This aqueous layer was ice-cooled and adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals.	50
55	The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 1.8 g of $6-[D(-)-\alpha-(4-a)]-3-\infty-1$ -piperazinocarbonylamino)-phenylacetamido]penicillanic acid, m.p. 92°C (decomp.), yield 90%.	55
60	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1760 (lactam), 1720—1620 (—COOH, —CON<) The above-mentioned operation was repeated, except that the 4-allyl-3-oxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 11, to obtain respective objective compounds as shown in Table 11. The structure of each objective compound was confirmed by IR and NMR.	60

Objective compound		HCONH SCH3 COOH COOH	HCONH CH3) 0 COOH		HCONH SCH3 COOH COOH Soc, yield 84 %
Objectiv		D(-)- 0 CH2=CHCH-N N-CONHCHCONH CH3 CH3 CH3 (decomp.) 102°C, yield 80 %	D(-)- CH2=CCH2-N N-CONHCHCONH CH3 CH3 CH3 CH2 CH2 CH2 CH2 CH3 CH3	4	D(-)- CH3CH HCCH2-N N-CONHCHCONH CH; CH; CH; N-CONHCHCONH COCH; N.p. (decomp.) 95°C, yield 84 %
Reactive derivative of	compound of formula (III)	CH2=CHCH-N N-COC1	о сн ₂ =ссн2-м м-сост сн ₃		CH3CH O HCCH2-N N-COC1 (trans-)

cont'd

Table 11 (Cont'd)

о сн ₃ (сн ₂) ₄ сн ₂ -м м-сос1	D(-)- 0 CH2 (CH2)4 CH2-N N-CONHCHCONH CH2 CH3 CH3 CH3 COOH
	m.p. (decomp.) 128 - 130°C, yield 97 %
сн ₃ (сн ₂) ₅ сн ₂ -мм-сос1	$D(-)- 0$ $CH_{2}(CH_{2})_{5}CH_{2}-M$ $CH_{$
сн ₃ (сн ₂) 6сн ₂ -м м-сост	D(-)- CH ₂ (CH ₂)6CH ₂ -N N-CONHCHCONH S CH ₃ CH ₂ CH ₃ (CH ₂)6CH ₂ -N S CH ₃ COOH m.p. (decomp.) 110°C, yield 98 %

cont. d

Table 11 (Cont'd)

сн ₃ (сн ₂) ₁₀ сн ₂ -м м-сос1	D(-)- CH ₃ (CH ₂) ₁₀ CH ₂ -N N-CONHCHCONH
E - N N-COCI	D(-)- (H)- NCONHCHCONH - S CH3 (O) 0 m.p. (decomp.) 134°C, yield 87 %
O-NHCO-N N-COCI	D(-)- O CONHCHCONH S CH2 O-NHCO-N N-CONHCHCONH CH2 O O O O O O O O O O O O O O O O O O O
	- cont'd

S

Table 11 (Cont'd)

B - 128°C, yield 79.5 (decomp.) 125 -CONHCHCONH -0 m.p. D(-)-

Using 0.63 g of 6-[D(-)- α -aminophenylacetamido]penicillanic acid and 600 mg of a hydrochloride of 4-(N-morpholinomethyl)-3-oxo-1-piperazinocarbonyl chloride, the same operation as in Example 6 was repeated to obtain 0.63 g of 6 - {D(-) - α - [4 - (N - morpholinomethyl) - 3 - oxo - 1 - piperazinocarbonylamino]phenylacetamido}penicillanic acid, m.p. 85°C (decomp.), yield 60%.

S

IR (KBr) cm⁻¹: v₀=₀: 1770 (lactam), 1600—1680 (—COO[⊙], —CON<)

Using 5.0 g of a hydrochloride of pivaloyloxymethyl ester of 6-[D(--)-\alpha-amino-phenylacetamido]penicillanic acid and 1.94 g of 2-methyl-3-oxo-1-piperazinocarbonyl chloride, the same operation as in Bxample 6 was repeated to obtain 5.2 g of a pivaloyloxymethyl ester of 6-[D(--)-\alpha-(2-methyl-3-oxo-1-piperazinocarbonylamino)phenyl-acetamido]penicillanic acid, m.p. 140°C (decomp.), yield 80%.

2

15 IR (KBr) cm⁻¹: vo=0 1740-1770 (lactam, ester) 1630-1670 (-CON<) 15

Example 9.

(1) Into a mixture comprising 8.0 g of 4-acetyl-2,5-dioxo-piperazine, 5.0 g of triethylamine and 100 ml of anhydrous tetrahydrofuran was dropped 6.0 g of trimethylchlorosilane with stirring at room temperature. After the dropping, the resulting mixture was reacted at said temperature for 2 hours to deposit triethylamine hydrochloride. The deposited hydrochloride was separated by filtration, and the filtrate was dropped at 0° to 5°C into 100 ml of an anhydrous tetrahydrofuran solution containing 10.0 g of phosgene. After completion of the dropping, the resulting mixture was stirred at 10°

	·	
102	1,508,062	102
	to 15°C for 3 hours to terminate the reaction. Subsequently, the tetrahydrofuran and the excess phosgene were removed by distillation under reduced pressure to obtain 11.0 g of oily 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride.	
5	(2) A suspension of 17.5 g of $6-[D(-)-\alpha$ -aminophenylacetamido] penicillanic acid in 200 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethyl amine with stirring at 10° to 15°C to form a homogeneous solution. Into this solution was dropped a solution of 11.0 g of the	5
	aforesaid 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride in 30 ml of tetrahydrofuran at 0°C over a period of 30 minutes. During this period, the pH of the reaction solution	•
10	was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the temperature of the resulting mixed solution was elevated to 5° to 10°C and the solution was further reacted for 1 hour while maintaining the pH thereof at 7.5 to 8.0 by addition of triethylamine. After completion of the reaction, the tetrahydrofuran was removed	10
15	by distillation under reduced pressure. To the residue was added 100 cc of N hydro- chloric acid at 0° to 10°C, and the resulting mixture was stirred for 30 minutes to	15
. 20	deposit white crystals. The deposited crystals were collected by filtration, and again suspended in water. The resulting aqueous suspension was adjusted to a pH of 8.0 by gradual addition of triethylamine at 5° to 10°C, and then freed from insolubles by filtration. The filtrate was adjusted to a pH of 1.5 by gradual addition of N-hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and then dried to obtain 21.2 g of $6-[D(-)-\alpha-(4-acetyl-2.5-dioxo-1-piperazino-carbonylamino)$ phenylacetamido]penicillanic acid, b.p. 162—164°C (decomp.), yield 80%.	20
25	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1770 (lactam), 1730—1660 (—COOH, —CON<) NMR ((CD ₃) ₂ CO) τ values: 0.23 (1H), 2.65 (5H), 4.26 (1H), 4.33—4.63 (2H), 5.38 (4H), 5.68 (1H), 7.55 (3H), 8.47 (3H), 8.53 (3H)	25 *
30	The above-mentioned operation was repeated, except that the 4-acetyl-2,5-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 12, to obtain respective objective compounds as shown in Table 12. The structure of each objective compound was confirmed by IR and NMR.	30

Table 12

Objective compound	D(-)- O-co-N N-CONHCHCONH SCH3 O O O COOH m.p. (decomp.) 88°C, yield 60 %	D(-)- O CH3-N N-CONHCHCONH S CH3 O O O M.p. (decomp.) 179 - 181°C, yield 83 %	D(-)- O-CH2-N N-CONHCHCONH SCH3 OOOH OOOOH OOOOOOOOOOOOOOOOOOOOOOOOO
Reactive derivative of compound of formula (III)	O-co-M N-cocı	CH3-N_N-COC1	O-CH2-N N-COC1

cont'd -

Table 12 (Cont'd)

HN N-COC1	D(-)- 0 (H) N-CONHGHCONH S (CH3) 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
HM N-coc1	D(-)- HW N-CONHCHCONH SCH2 O O O O O O O O O O O O O O O O O O O
HN N-COC1	D(-)- O(CH ₃ HN N-CONHCHCONH S CH ₃ O (O) O (O) O (O) O (O) N.p. (decomp.) 148 - 151°C, yield 92 %
	D. #400

cont.d

Table 12 (Cont'd)

O H O CH2-N N-COCI	D(-)- O(H) O-CH2-N-CONHCHCONH O(O)-CH2-N-COOH O(O)-N-COOH O(O)-N-C
Cl3CCH2OCO-N N-COCL	D(-)- C1 ₃ CCH ₂ OCO-N N-CONHCHCONH SCH ₃ C1 ₃ CCH ₂ OCO-N N-CONHCHCONH CH ₃ O (A) M.p. (decomp.) 120 - 125°C, yield 92 %
O-CH2-N N-COC1	D(-)- OCH2-N N-CONHCHCONH S CH3 OCH2-N N-CONHCHCONH COH3 OCH2-N N-CONHCHCONH SOM OCH3 OCH2-N N-CONHCHCONH SOM OCH3

106	1,508,062	106
5	Example 10. (1) A suspension of 8.0 g of D(-)-α-aminophenyl acetic acid in 80 ml of tetrahydrofuran was adjusted to a pH of 11.5 by gradual addition of a N sodium hydroxide solution with stirring to form a homogeneous solution. This solution was cooled to 0°C, and 15 ml of a tetrahydrofuran solution containing 11 g of 4-acetyl-2,5-dioxo-1-piper-	5
3	azinocarbonyl chloride was dropped at said temperature into said solution over a period of 30 minutes. During this period, the pH of the reaction solution was maintained at 10.5 to 11.0 by gradual addition of a N sodium hydroxide solution. Subsequently, the temperature of the resulting mixed solution was elevated to 5° to 10°C, and the mix-	a a
10	ture was further reacted for 1 hour, upon which $D(-)-\alpha$ -aminophenylacetic acid deposited. After completion of the reaction, the deposited acid was separated by filtration, and the filtrate was concentrated under reduced pressure to remove tetrahydrofuran. The residue was dissolved in a mixed solvent comprising 10 ml of water and 80 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.0 by addi-	10
	tion of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, dried over anhydrous magnesium sulfate, and then charged into 100 ml of an ethyl acetate solution containing 8.3 g of sodium 2-ethylhexanoate to deposit crystals. The deposited crystals were collected by filtration, washed with acetone, and then dried over P_2O_5 to obtain 7.9 g of a sodium salt of $D(-)-\alpha-(4-acetyl-2,5-dioxo-based)$	15
20	1-piperazinocarbonylamino)phenylacetic acid, m.p. 104°C (decomp.), yield 42%. IR (KBr) cm ⁻¹ : ν _{C=0} 1690—1650, 1600—1590	20
	(2) To a suspension in 25 ml of anhydrous acetone of 1.75 g of the aforesaid	
25	sodium salt of $D(-)-\alpha$ -(4-acetyl-2,5-dioxo-1-piperazinocarbonylamino)phenylacetic acid was added 20 mg of N-methylmorpholine, and the resulting mixture was cooled to -20° to -15° C. Into this mixture was dropped a solution of 0.57 g of ethyl chloro-	25
#	carbonate in 5 ml of anhydrous acetone over a period of 5 minutes, and the mixture was stirred at said temperature for 60 minutes. Subsequently, a solution of 1.29 g of a triethylamine salt of 6-aminopenicillanic acid in 30 ml of anhydrous methylenechloride was dropped into said mixture at -40° to -30° C over a period of 10 minutes. The	
30	temperature of the resulting mixture was elevated from -30°C to 0°C, and the mixture was then reacted at said temperature for about 2 hours. After the reaction, the solvent was removed by distillation under reduced pressure. The residue was charged into 30 ml of water, and the resulting mixture was freed from insolubles by filtration with ice-cooling. The filtrate was adjusted to a pH of 1.5 to 2.0 by addition of dilute hydro-	30
35	chloric acid to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water, and then dried to obtain 2.34 g of $6 \cdot [D(-) - \alpha \cdot (4-\text{acetyl-2,5-dioxo-1-piperazinocarbonylamino})$ phenylacetamido] penicillanic acid, m.p. 162—164°C (decomp.), yield 90%. In the same manner as above, 530 mg of $6 \cdot [D(-) - \alpha \cdot (4-\text{benzyl-2,2-pentamethyl-piperazinocarbonylamino})$	35
40	ene-3,5-dioxo-1-piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 95—100°C, yield 82.68%, was obtained from 450 mg of $D(-)-\alpha$ -(4-benzyl-2,2-pentamethylene-3,5-dioxo-1-piperazinocarbonylamino)phenylacetic acid and 320 mg of a triethylamine salt of 6-amino-penicillanic acid.	40
	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1770 (lactam), 1700—1660 (—COOH, —CON<)	
45	Example 11. (1) Into a mixture comprising 8 g of a diethyl ester of oxalic acid and 8 ml of ethanol was dropped at room temperature 4.4 g of N-ethyl ethylenediamine. The resulting mixture was allowed to react for 3 hours, and then heated to remove the ethanol.	45
50	Subsequently, the residue was recrystallized from 10 ml of dioxane to obtain 5.4 g of 1-ethyl-2,3-dioxo-piperazine, m.p. 124°C, yield 76.0%. (2) To a suspension of 0.71 g of the above-mentioned 1-ethyl-2,3-dioxo-piperazine in 15 ml of anhydrous dioxane were added with stirring 0.70 g of trimethylsilyl chloride and 0.83 ml of triethylamine. The resulting mixture was stirred at room tem-	50
55	perature for 20 hours to deposit triethylamine hydrochloride. This hydrochloride was separated by filtration, and the filtrate was dropped at 5° to 10°C into a solution of 0.70 g of phosgene in 10 ml of anhydrous tetrahydrofuran. Subsequently, the resulting mixture was reacted at 5° to 10°C for 30 minutes and at room temperature for 2 hours, and then the solvent was removed by distillation under reduced pressure to obtain 1.0 g of pale yellow crystals of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride.	55

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	(3) A suspension of 1.75 g of 6-[D(-)- α -aminophenylacetamido] penicillanic acid in 50 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This	
4	solution was cooled to 0° to 5°C, and then 7 ml of an anhydrous tetrahydrofuran solu-	
5	tion containing 1.0 g of the aforesaid 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride was dropped into the solution. During this period, the pH of the reaction solution was	5
•	maintained at 7.5 to 8.0 by gradual addition of triethylamine. The resulting mixed solution was reacted at said temperature for 30 minutes and then at 5° to 10°C for 1 hour,	
	while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the tetrahydrofuran	
10	was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. To the aqueous	10
	layer was again added 50 ml of ethyl acetate, and the resulting mixture was adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subse-	
	quently, the ethyl acetate layer was separated off, sufficiently washed with water, and	15
15	then dried over anhydrous magnesium sulfate. Into the thus treated layer was dropped 10 ml of an ethyl acetate solution containing 0.83 g of sodium 2-ethyl-hexanoate to deposit white crystals. The deposited crystals were collected by filtration, sufficiently	13
	washed with ethal acetate, washed with diethal ether, and then dried to obtain 2.4 g of	
	a sodium salt of $6-[D(-)-\alpha-(4-\text{ethyl}-2,3-\text{diox}o-1-\text{piperazinocarbonylamino})$ phenyl-	20
20	acetamido] penicillanic acid, m.p. 183—185°C (decomp.), yield 89%.	20
	IR (KBr) cm ⁻¹ : $\nu_{O=0}$ 1765 (lactam), 1720—1670 (—CON<), 1600 (—COO [©]) NMR ((CD ₈) ₂ SO+D ₂ O) τ values: 2.62 (5H), 4.31 (1H), 4.50 (1H), 4.70 (1H), 6.05 (1H), 6.35—6.65 (6H), 8.49 (3H), 8.60 (3H), 8.91 (3H)	
	The above-mentioned operation was repeated, except that the 4-ethyl-2,3-dioxo-	25
25	1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of com- pounds of formula (III) shown in Table 13, to obtain respective objective compounds as shown in Table 13. The structure of each objective compound was confirmed by IR	25
	and NMR.	

Table 13

Reactive derivative of compound of formula (III)	Objective compound
0 0 CH3-N N-COC1	D(-)- CH3-N N-CONHCHCONH SCH3
	m.p. (decomp.) 170°C, yield 84 %
CH3CH2-N N-COC1	D(-)- CH3CH2CH2-N N-CONHCHCONH SCH3 CH3CH2CH2-N N-CONHCHCONH CHCONH
	m.p. (decomp.) 170°C, yield 86 %
0 0 0 0 0H3(CH2)2CH2-N N-COCI	D(-)- CH ₃ (CH ₂) ₂ CH ₂ -N CH ₃ (CH ₂) ₂ CH ₂ -N CONHCHCONH COONB
	m.p. (decomp.) 190°C, yield 87 %

Table 13 (Cont'd)

(сн ₃)2сн-й_м-сос1	D(-)- 0 0 (CH ₃) ₂ CH-N N-CONHCHCONH CH ₃ CH ₃ (CH ₃ (CH ₃ C) 0 (O)
о о сн ₃ соосн ₂ сн ₂ -и и -сос1	D(-)- CH ₃ COOCH ₂ CH ₂ -N N-CONHCHCONH S CH ₃ (O) M.p. (decomp.) 175°C, yield 79 %
сн2=снсн2-м м-сост	$D(-)- 0 0 0$ $CH_2=CHCH_2-N N-CONHCHCONH S CH_2$ $O O O CH_3$ $O O O CH_4$ $O O O O O O O O CH_4$ $O O O O O O O O O O O O O O O O O O O $

Table 13 (Cont'd)

0 - N N - COC1	D(-)- O-N N-CONECHCONE S CH3 O-N N-CONECHCONE S CH3 COONA M.p. (decomp.) 185 - 187°C, yield 88 %
ClcH2CH2-N N-COCl	D(-)- ClCH2CH2-N N-CONHCHCONH COONB CLCH2CH2-N N-CONHCHCONH COONB CLCH2CH2-N N-CONHCHCONH CLCH2CH2-N N-COONB ClCH2CH2-N N-CONHCHCONH ClCH2CH2-N N-COONB ClCH2CH2-N N-CONHCHCONH CLCH2CH2-N N-CONHCHCON
оо СН ₃ СН2-и и-сосл СН ₃	$D(-) CH_3CH_2-N$ CH_3 CH_3 CH_3 CH_3 CH_3 O

Table 13 (Cont'd)

D(-)OOO
CH3-N N-CONHCHCONH S CH3
CH3 OOO COONA
m.p. (decomp.) 177 - 178°C, yield 79 %

Example 12.

was cooled to 0° to 5°C, and 10 ml of a tetrahydrofuran solution containing 1.2 g of 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride was dropped into said solution. A suspension of 1.4 g of 6-[D(-)-c-aminophenylacetamido] penicillanic acid in 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution gradual addition of triethylamine. Subsequently, the resulting mixed solution was reacted at said temperature for 30 minutes and then at 10° to 15°C for 90 minutes, while maintaining the pH thereof at 7.5 to 8.5. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. To the aqueous to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Thereafter, the 30 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of The residue was crystallized by addition of disopropyl ether to obtain 1.8 g of crystals During this period, the pH of the reaction solution was maintained at 7.5 to 8.5 by layer was further added 30 ml of ethyl acetate, and the resulting mixture was adjusted of $6 - [D(-) - \alpha - (4 - n - pentyl - 2, 3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid, m.p. 96°C (decomp.), yield 80.5%.$ ethyl acetate layer was separated off, sufficiently washed with water, dried over magnesium sulfate, and then freed from the solvent by distillation under reduced pressure ន 15 2

IR (KBr) cm⁻¹: "_{Vo=0} 1770 (lactam), 1720—1660 (—CON<, —COOH) NMR ((CD₃)₂SO+D₂O) τ values: 2.62 (5H), 4.31 (1H), 4.51—4.69 (2H), 6.04 (1H), 6.20—6.90 (6H), 8.50 (3H), 8.60 (3H), 8.75 (6H), 8.90 (3H) The above-mentioned operation was repeated, except that the 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 14, to obtain respective objective compounds as shown in Table 14. The structure of each objective compound was confirmed by IR and NMR.

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Reactive derivative of compound of formula (III) OOO CH ₂ (CH ₂) ₄ CH ₂ -NN-COC1	Objective compound D(-)- OOO CH3(CH2)4CH2-N N-CONHCHCONH SCH3 CH3(CH2)4CH2-N N-CONHCHCONH CH3 OOO m.p. (decomp.) 107°C, yield 89 %
оо сн ₃ (сн ₂) ₅ сн ₂ -м м-сос1	D(-)- CH ₂ (CH ₂) ₅ CH ₂ -N N-CONHCHCONH SG, SCH ₂ CH ₃ CH ₂ CH ₃ CH
сн ₃ (сн ₂) ₆ сн ₂ -мм-сос1	D(-)- CH ₃ (CH ₂) ₆ CH ₂ -N N-CONHCHCONH

S

(Cont'd) Table 14

pç. 95 - 82°C, yield m.p. (decomp.) 80 (-) A

Example 13. Using 1.7 g of a triethylamine salt of $6-[D(-)-\alpha$ -amino-p-hydroxyphenylacetamido] penicillanic acid and 0.7 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 11 was repeated to obtain 1.2 g of a sodium salt of 6 - $[D(-) - \alpha - (4 - methýl - 2,3 - díoxo - 1 - piperazinocarbonylamino) - p-hydroxyphenylacetamido] penicillanic acid, m.p. 170—172°C (decomp.), yield 75%.$ (-)Q(-)

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IR (KBr) cm⁻¹: $v_{0=0}$ 1760 (lactam), 1710—1660 (—CON <), 1600 (—CO0 $^{\oplus}$) NMR ((CD₈),SO) τ values: 2.8—3.3 (4H), 4.45 (1H), 4.65 (2H), 6.05 (1H), 6.2 (4H), 6.97 (3H), 8.48 (3H), 8.60 (3H)

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In the same manner as above, a sodium salt of $6-[D(-)-\alpha-(4-\text{ethyl-}2,3-\text{dioxo-}1-\text{piperazinocarbonylamino})$ -p-hydroxyphenylacetamido]penicillanic acid, m.p. 175°C (decomp.), yield 72%, was obtained from 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride and a triethylamine salt of $6-[D(-)-\alpha-\text{amino-p-hydroxyphenylacetamido}]$ penicillanic acid.

residue was dissolved in a mixed solvent comprising 20 ml of ethyl acetate and 20 ml of water, and the resulting solution was adjusted to a pH of 2 by addition of dilute hydrochloric acid. Subsequently, the organic layer was separated off, washed with water, washed with a 2% aqueous sodium hydrogenocarbonate solution, washed with water, Example 14.

To a solution of 0.8 g of a phthalide ester of 6-[D(-)-x-aminophenylacetamido]-penicillanic acid in 10 ml of tetrahydrofuran was added 0.25 ml of triethylamine. Into the resulting mixture was dropped 0.32 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride with ice-cooling, and the mixture was reacted at room temperature for 2 hours. After the reaction, the solvent was removed by distillation under reduced pressure. The

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dried over magnesium sulfate, and then concentrated to a liquid amount of about 2 ml. To the concentrate was added 20 ml of diisopropyl ether to deposit crystals, which were then collected to obtain 0.95 g of crystals of a phthalide ester of $6-[D(-)-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)$ phenylacetamido] penicillanic acid, m.p. 157—160°C (decomp.), yield 90.0%.

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IR (KBr) cm⁻¹: $\nu_{0=0}$ 1780 (lactam), 1715 (ester), 1680 (—CON<) NMR ((CD₈)₂CO₁+D₂O) τ values: 2.12 (4H), 2.40 (1H), 2.58 (5H), 4.25—4.60 (3H), 5.45 (1H), 5.85—6.42 (4H), 6.90 (3H), 8.50 (6H)

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The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 15, to obtain respective objective compounds as shown in Table 15. The structure of each objective compound was confirmed by IR and NMR

Table 15

Reactive derivative of compound of formula (III)	Objective compound
CH ₃ CH ₂ -N N-COC1	D(-)- CH ₃ CH ₂ -N -CONHCHCONH S CH ₃ 9 0 0
	m.p. (decomp.) 108 - 110°C, yield 90 %
(CH ₃) ₂ CH-N N-COC1	D(-)- CH3)2CH-N N-CONHCHCONH SCH3 CH3 CH3)2CH-N N-CONHCHCONH CONHCHCONH
	m.p. (decomp.) 128 - 130°C, yield 92 %
CH3(CH2)2CH2-N N-COC1	D(-)- CH2 CH2)2CH2-N N-CONHCHCONH S CH3 O O O CH3 (CH2) 2CH2 O O O O O O O O O O O O O O O O O O O
	m.p. (decomp.) 113 - 115°C, yield 88 %

and NMR.

Example 15. A solution of 0.86 g of a hydrochloride of methoxymethyl ester of 6-[D(-)-aaminophenylacetamido]penicillanic acid in 15 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine at 0° to 5°C. Into this solution, a solution of 0.38 g of 4-methyl-2,3-dioxo-1-piperazino-5 carbonyl chloride in 10 ml of tetrahydrofuran was dropped over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. The resulting mixed solution was reacted for 30 minutes, while maintaining the pH thereof at 7.5 to 8.0. After completion of the reac-10 tion, the tetrahydrofuran was removed by distillation under reduced pressure. The 10 residue was dissolved in a mixed solvent comprising 50 ml of water and 50 ml of ethyl acetate, and the resulting solution was adjusted to a pH of 1.5 by addition of dilute hydrochloric acid with ice-cooling. Subsequently, the organic layer was separated off, washed with water, dried over anhydrous magnesium sulfate, and then freed from the solvent by distillation under reduced pressure to form crystals. The thus formed crystals 15. 15 were washed with diethyl ether to obtain 0.9 g of a methoxymethyl ester of 6-[D(-)α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetamido] penicillanic acid, m.p. 111-115°C (decomp.), yield 82.5%. IR (KBr) cm⁻¹: $\nu_{C=0}$ 1780 (lactam), 1740 (ester), 1700—1660 (—CON<) NMR ((CD₂)₂CO) τ values: 0.15 (1H), 2.0 (1H), 2.67 (5H), 4.3—4.5 (3H), 4.75 (2H), 5.7 (1H), 6.55 (4H), 6.97 (3H), 7.25 (3H), 8.84 (3H), 8.60 (3H) 20 20 The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of com-25 pounds of formula (III) shown in Table 16, to obtain respective objective compounds 25 as shown in Table 16. The structure of each objective compound was confirmed by IR

Table 16

Reactive derivative of	
compound of formula (III)	Objective compound
CH ₃ CH ₂ -N N-COC1	D(-)- CH ₃ CH ₂ -N N-CONHCHCONH SCH ₃ CH ₃ CH ₂ O CH ₃ CH ₂ -N COOCH ₂ OCH ₃ O D D O CH ₃ CH ₂ O CH ₃ CH ₃ O CH ₃ CH ₂ O CH ₃ CH ₂ O CH ₃ CH ₃ O C C C C C C C C C C C C C C
сн ₃ (сн ₂) ₂ сн ₂ -м м-сост	D(-)- CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH S CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH CH ₃ CH ₃ CH ₃ CH ₃ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH CH ₃
0 0 (СН ₃) ₂ СН-М М-СОС1	D(-)- OOO (CH3)2CH-N M-CONHCHCONH SCH3 (CH3)2CH-N M-CONHCHCONH OOO OOO M.p. (decomp.) 93 - 95°C, yield 82.5 %

Table 16 (Cont'd)

	D(-)-
оо сн ₃ (сн ₂) ₆ сн ₂ -и м-сос1	CH ₃ (CH ₂) ₆ CH ₂ -N N-CONHCHCONH
	m.p. (decomp.) 70 - 74°C, yield 74.4 %

Using 1.5 g of a hydrochloride of pivaloyloxymethyl ester of $6 \cdot [D(-)$ -a-aminophenylacetamido] penicillanic acid and 0.6 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 15 was repeated to obtain a pivaloyloxymethyl ester of $6 \cdot [D(-)$ -a-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido] penicillanic acid, m.p. 108—11°C (decomp.), yield 75%.

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IR (KBr) cm⁻¹: "0=0 1780 (lactam), 1750 (ester), 1710-1660 (-CON<)

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 17, to obtain respective objective compounds as shown in Table 17. The structure of each objective compound was confirmed by IR and NMR.

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Table	

Reactive derivative of compound of formula (III)	Objective compound
	D(-)-
CH3CH2-N N-COCI	CH ₃ CH ₂ -N N-CONHCHCONH S CH ₃ CH
	m.p. (decomp.) 94 - 98°C, yield 77 %
	D(-)-
CH ₂ (CH ₂) ₆ CH ₂ -N N-COC1	CH ₂ (CH ₂)6CH ₂ -N N-CONHCHCONH S CH ₃ CH ₃ (CH ₂)6CH ₂ -N N-CONHCHCONH CH ₃
	m.p. (decomp.) 72 - 75°C, yield 72 %

Using 0.81 g of a hydrochloride of β -piperidinoethyl ester of 6-[D(-)- α -aminophenylacetamido)penicillanic acid and 0.3 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 15 was repeated to obtain 0.75 g of a β -piperidinoethyl ester of 6-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-phenylacetamido]penicillanic acid, m.p. 166—169°C (decomp.), yield 78%.

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IR (KBr) cm⁻¹: "0-0 1780 (lactam), 1740 (ester), 1710—1670 (—CON<) NMR (CDCl₈) r values: 2.7 (5H), 4.3—4.6 (3H), 5.7 (1H), 5.75 (2H), 6.0 (2H), 6.4 (2H), 6.9 (3H), 7.45 (2H), 7.6 (4H), 8.5 (12H)

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The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by 4-n-octyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a \(\theta\)-piperidinoethyl ester of \(\theta\)-\(\thet (decomp.), yield 73.58%.

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5	Example 18. Using 0.93 g of a hydrochloride of β -morpholinoethyl ester of 6-[D(-)- α -aminophenylacetamido] penicillanic acid and 0.39 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 15 was repeated to obtain 0.8 g of a β -morpholinoethyl ester of 6-[D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonyl-amino)phenylacetamido] penicillanic acid, m.p. 150—153°C (decomp.), yield 73%.	<i>i</i> 5 [°] €
	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1780 (lactam), 1740 (ester), 1710—1680 (—CON<) NMR (CDCl _s) τ values: 2.55 (5H), 4.3—4.55 (3H), 5.6 (1H), 5.7 (3H), 6.0 (2H), 6.3 (2H), 7.4 (2H), 7.5 (4H), 8.5 (6H)	•
10	The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by 4-n-octyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a β -morpholinoethyl ester of 6- $[D(-)-\alpha-(4-n-octyl-2,3-dioxo-1-piperazinocarbonylamino)$ phenylacetamido]penicillanic acid, m.p. 103—105°C (decomp.), yield 70%.	10
15	Example 19. (1) To a solution of 8.7 g of a sodium salt of D(-)-\alpha-phenylglycine in 50 ml of water were added 50 ml of ethyl acetate and 5.05 g of triethylamine. To the resulting mixture was gradually added 9.5 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride at 0° to 5°C over a period of 15 minutes, and then the mixture was reacted at 5° to	15
20	15°C for 30 minutes. After the reaction, the aqueous layer was separated off, washed with diethyl ether, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit crystals. The deposited crystals were collected by filtration, washed with water and dried to obtain 14.1 g of $D(-)-\alpha-(4-\text{methyl-}2,3-\text{diox}o-1-\text{piperazinocarbonyl-amino})$ phenylacetic acid, m.p. 138—141°C (decomp.), yield 87%. Recrystallization	20
25	from hydrous butanol gave white crystals, m.p. 140—142°C (decomp.).	25
	Elementary analysis (for $C_{14}H_{15}N_3O_3$. H_2O): Calculated (%) C: 52.01 H: 5.30 N: 13.00 Found (%) C: 52.24 H: 5.32 N: 12.87 IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1710, 1700, 1660	
30	(2) Into a solution of 10 g of the above-mentioned $D(-)-\alpha$ -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid in 200 ml of acetone was dropped a solution of 5.2 g of a sodium salt of 2-ethylhexanoic acid in 50 ml of acetone with stirring to deposit crystals. The deposited crystals were collected by filtration and then washed with acetone to obtain 9.6 g of a sodium salt of $D(-)-\alpha$ -(4-methyl-2,3-dioxo-	30
35	1-piperazinocarbonylamino) phenylacetic acid, m.p. 165°C (decomp.), yield 95%. (3) To a suspension of 8.8 g of the above-mentioned sodium salt of D(—)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid in 80 ml of methylene chloride was added 20 mg of N-methylmorpholine. Into the resulting mixture was	35
40	dropped a solution of 3.1 g of ethyl chlorocarbonate in 20 ml of methylene chloride at -20° to -15°C over a period of 5 minutes, and the mixture was reacted at said temperature for 1 hour. Into this reaction liquid was dropped a solution of 9.4 g of a triethylamine salt of 6-aminopenicillanic acid in 40 ml of methylene chloride at -40° to -30°C over a period of 10 minutes, and the resulting mixture was reacted at -40° to -20°C over a period of 1 hour. After the reaction, the temperature of the reaction	40
45	liquid was gradually elevated to 0°C over a period of 1 hour, and the mixture was then subjected to extraction with 100 ml of water. Subsequently, the aqueous layer was separated off, and the methylene chloride layer was further subjected to extraction with	45
50	50 ml of water, and the resulting aqueous layer was combined with the aforesaid aqueous layer. The combined aqueous layer was adjusted to a pH of 2 by addition of dilute hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration, sufficiently washed with water, dried and then dissolved in 200 ml	50
55	of acetone. Into the resulting solution was dropped a solution of 4 g of a sodium salt of 2-ethylhexanoic acid in 40 ml of acetone over a period of 10 minutes to deposit crystals. The deposited crystals were collected by filtration, washed with acetone and then dried to obtain 11.4 g of a sodium salt of $6-[D(-)-\alpha-(4-\text{methyl-2,3-dioxo-1-piperazino-carbonylamino})$ phenylacetamido] penicillanic acid, m.p. 170°C (decomp.), yield 80.8%. The above-mentioned operation was repeated, except that the $D(-)-\alpha-(4-\text{methyl-decomp.})$	55
. 60	2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 18, to obtain respective objective compounds as shown in Table 18. The structure of each objective compound was confirmed by IR and NMR.	. 60

Table 18

Compound of formula (V)	Objective compound
D(-)-	D(-)-
сн3сн2-и и-сомнснсоон	CH ₂ CH ₂ -N N-CONHCHCONH SCH ₂ CH ₃ CH ₂ -N N-CONHCHCONH CH ₃ CH ₃ CH ₂ -N COONe
D(-)-	D(-)-
CH ₂ CH ₂ CH ₂ -N_N-CONHCHCOOH	CH ₂ CH ₂ CH ₂ -N N-CONHCHCONH S CH ₃ CH ₂ CH ₂ CH ₂ -N N-CONHCHCONH CH ₂ CH ₃ CH ₂ CH ₂ CH ₂ -N N-CONHCHCONH CH ₂ CONH
D(-)-	D(-)-
сн ₃ (сн ₂) ₂ сн ₂ -и и-соинсисоон	CH ₂ (CH ₂) ₂ CH ₂ -N N-CONHCHCONH S CH ₂ (O) 0 CONA

5	Bxample 20. (1) To a solution of 2.28 g of $D(-)$ - α -amino-1,4-cyclohexadienylacetic acid in 15 ml of N NaOH were added 20 ml of ethyl acetate and 2.1 ml of triethylamine, and the resulting mixture was cooled to 0°C. To this mixture was gradually added 1.69 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. Subsequently, the mixture was reacted for 30 minutes with ice-cooling, and then the aqueous layer was separated off. To the aqueous layer was further added 20 ml of ethyl acetate. The resulting mixture was adjusted to a pH of 2 by addition of 2N hydrochloric acid with ice-cooling, and the ethyl acetate layer was separated off. The organic layer was sufficiently washed with water, dried over anhydrous magnesium sulfate, freed from the solvent by distillation under reduced pressure and then incorporated with isopropyl alcohol to deposit crystals. The deposited crystals were collected by filtration to obtain 2.5 g of white crystals of $D(-)$ - α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid, m.p. 140—145°C (decomp.), yield 74%.	5
15	IR (KBr) cm ⁻¹ : ν_{NH} 3300, $\nu_{C=0}$ 1715, 1660 NMR (d ₆ -DMSO) τ values: 0.57 (1H, d), 4.26 (1H, s), 4.36 (2H, s), 5.29 (1H, d), 6.07—6.18 (2H, m), 6.38—6.49 (2H, m), 7.05 (3H, s), 7.35 (4H, s)	15
20	(2) To a suspension of 0.45 g of the above-mentioned $D(-)-\alpha$ -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-1,4-cyclohexadienylacetic acid in 15 ml of anhydrous methylene chloride was added 0.24 ml of N-methylmorpholine with stirring to form a solution. After cooling the solution of -10° C, 3 ml of an anhydrous methylene chloride solution containing 0.24 g of ethyl chlorocarbonate was dropped into the solution, and	20
25	the resulting mixture was reacted at said temperature for 90 minutes. Subsequently, the reaction liquid was cooled to -20° C, and 5 ml of a methylene chloride solution containing 0.70 g of a triethylamine salt of 6-aminopenicillanic acid and 0.31 ml of triethylamine was gradually dropped into the reaction liquid. The resulting mixture was reacted at -20° C for 1 hour, at -20° to 0° C for 1 hour, and at 0° to 0° C for 1 hour. Thereafter, the reaction liquid was freed from the solvent by distillation under reduced	25
30 35	pressure. The residue was dissolved in 10 ml of water and then washed with 10 ml of ethyl acetate. The aqueous layer was again incorporated with 15 ml of ethyl acetate, and then adjusted to a pH of 2.0 by addition of 2N HCl with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, dried over anhydrous magnesium sulfate, and freed from the solvent by distillation under reduced pressure to obtain 0.74 g of white crystals of $6-[D(-)-\alpha-(4-\text{methyl-}2,3-\text{dioxo-}1-\text{piperazino-}1]$	30
33	carbonylamino)-1,4-cyclohexadienylacetamido] penicillanic acid, m.p. 84—87°C (decomp.), yield 87%. IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1780 (lactam), 1730—1660 (—COOH, —CON<)	
40	NMR (d ₈ -DMSO) τ values: 0.55 (1H, d), 0.95 (1H, d), 4.22 (1H, s), 4.35 (2H, s), 4.41—4.61 (2H, s), 4.92 (1H, d), 5.75 (1H, s), 6.05 (2H, bs), 6.40 (2H, bs), 7.03 (3H, s), 7.35 (4H, s), 8.40 (3H, s), 8.52 (3H, s) The thus obtained product was adjusted to a pH of 7.0 by neutralization with an	40
45	aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt thereof. The above-mentioned operation was repeated, except that the $D(-)-\alpha-(4-\text{methyl-2,3-dioxo-1-piperazinocarbonylamino})-1,4-cyclohexadienylacetic acid was replaced by each of the compounds of formula (V) shown in Table 19, to obtain respective objective compounds as shown in Table 19. The structure of each objective compound was confirmed by IR and NMR.$	45

Table 19

Compound of formula (V)	Objective compound
D(-)- 0 0 СН3СН2-И И-СОИНСНСООН	D(-)- CH ₂ CH ₂ -N N-CONHCHCONH S CH ₂ CH ₃ CH ₂ -N N-CONHCHCONH COONA
D(-)- CH3CH2CH2-N N-CONHCHCOOH	D(-)- CH ₂ CH ₂ CH ₂ -N N-CONHCHCONH S CH ₂ CH ₃ CH ₂ CH ₃ CH ₃ CH ₂ CH ₃ CH ₃ CH ₂ CH ₂ CH ₃
D(-)- CH ₂ (CH ₂) ₂ CH ₂ -N N-CONHCHCOOH	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

	Example 21.	
•	(1) To a solution of 2.2 g of DL- α -amino-2-thienylacetic acid in 14 ml of a N sodium hydroxide solution was added at 0°C 2.2 g of triethylamine. To the resulting mixture was further added 3.6 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride	a
5	little by little at said temperature. Subsequently, the mixture was reacted at 0°C for 30	5
	minutes, and then at room temperature for 30 minutes. After the reaction, the reaction liquid was adjusted to a pH of 1.0 by addition of dilute hydrochloric acid to deposit	•
	crystals. The deposited crystals were collected by filtration, washed with water and then	•
10	dried to obtain 3.5 g of DL-\a-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid, m.p. 214—215°C (decomp.), yield 80.5%.	. 10
	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1710, 1680—1660 (2) Into a solution of 3.5 g of the above-mentioned DL- α -(4-methyl-2,3-dioxo-	
	1-piperazinocarbonylamino)-2-thienylacetic acid in 100 ml of acetone was dropped a	
15	solution of 1.86 g of a sodium salt of 2-ethylhexanoic acid in 50 ml of acetone, upon which crystals were deposited. The deposited crystals were collected by filtration and	15
13	then washed with acetone to obtain 3.5 g of a sodium salt of DL- α -(4-methyl-2,3-	
	dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid, m.p. 175—176°C (decomp.). (3) To a suspension of 3.3 g of the above-mentioned sodium salt of DL-α-(4-	
0.0	methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid in 50 ml of methyl-	20
20	ene chloride was added 30 mg of N-methylmorpholine, and the resulting mixture was then cooled to -20° to -15° C. Into the resulting mixture was dropped a solution of	
	1.3 g of ethyl chlorocarbonate in 20 ml of methylene chloride over a period of 5 minutes,	
	and the mixture was stirred at said temperature for 90 minutes. Subsequently, a solution of 3.3 g of a triethylamine salt of 6-aminopenicillanic acid in 50 ml of methylene	
25	chloride was dropped into the mixture at -50° to -40° C over a period of 20 minutes, and the resulting mixture was reacted with stirring at -40° to -30° C for 30 minutes,	25
	at -30° to -20° C for 30 minutes, and then at -20° to 0° C for 30 minutes. After	
	the reaction, the solvent was removed by distillation under reduced pressure, and the residue was dissolved in water. The resulting aqueous solution was adjusted to a pH of	
30	2.0 by addition of dilute hydrochloric acid with ice-cooling to deposit crystals. The	30
	deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.1 g of 6-[DL-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-	
	thienylacetamido] penicillanic acid, m.p. 185°C (decomp.), yield 80.5%.	
	IR (Nujol Registered Trade Mark) cm ⁻¹ : $\nu_{C=0}$ 1780 (lactam), 1715 (—COOH),	
35	1685-1675 (—CON<) NMR ((CD ₃) ₂ CO) τ values: 0.5 (1H), 1.8 (1H), 2.6 (1H), 2.85—3.05 (2H),	35
	4.0 (1H), 4.2—4.5 (2H), 5.7 (1H), 5.8—6.0 (2H), 6.2—6.4 (2H),	
	6.95 (3H), 8.4 (3H), 8.45 (3H)	
40	The thus obtained product was adjusted to a pH of 7.0 by neutralization with an	40
70	aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze- drying to obtain a sodium salt thereof.	40
	The above-mentioned operation was repeated, except that the sodium salt of DL- \(\alpha\)-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)-2-thienylacetic acid was replaced	
45	by each of the compounds of formula (V) shown in Table 20, to obtain respective	
45	objective compounds as shown in Table 20. The structure of each objective compound was confirmed by IR and NMR.	45
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	Example 22.	
•	To a suspension of 0.9 g of $6-[D(-)-\alpha$ -aminophenylacetamido]penicillanic acid in 30 ml of anhydrous ethyl acetate were added at 5° to 10°C 0.55 g of triethylamine and 0.6 g of trimethylsilyl chloride. The resulting mixture was reacted at 15° to 20°C	2
5	for 3 hours to form trimethylsilylated $6-[D(-)-\alpha-aminophenylacetamido]$ penicillanic	5
	acid. To this acid was then added 1 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, and the resulting mixture was reacted at 15° to 20°C for 2 hours. After the reaction, a deposited triethylamine hydrochloride was separated by filtration, and the	F
10	filtrate was incorporated with 0.4 g of n-butanol to deposit crystals. The deposited crystals were collected by filtration to obtain 1.25 g of white crystals of $6-[D(-)-\alpha]$	10
10	(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetamido penicillanic acid. Into a solution of said crystals in 30 ml of tetrahydrofuran was dropped a solution of 0.38 g of a sodium salt of 2-ethylhexanoic acid in 10 ml of tetrahydrofuran, upon which white	
15	crystals were deposited. The deposited crystals were collected by filtration, sufficiently washed with tetrahydrofuran and then dried to obtain 1.25 g of a sodium salt of	15
	6 - $[D(-)$ - α - $(4$ - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid, m.p. 183—185°C (decomp.), yield 90%.	
	Example 23.	
20	To a suspension of 4 g of a trihydrate of 6-[D(-)-\alpha-aminophenylacetamido]-penicillanic acid in 40 ml of water was added 20 ml of ethyl acetate, and the resulting mixture was cooled to 2°C. Subsequently, the mixture was incorporated with 1.37 g of potassium carbonate, and then stirred at 2° to 3°C for 2 minutes. Thereafter, 1.89 g of	20
	A-methyl-2 3-dioyo-1-piperazipocarbonyl chloride was added to the mixture at said	
25	temperature over a period of 10 minutes, and the resulting mixture was reacted at said temperature for 15 minutes. After the reaction, slight amounts of insolubles were separ-	25
	ated by filtration, and the filtrate was charged into 80 ml of ethyl acetate. Into the resulting mixture was dropped 5 ml of 2N HCl at 20° to 22°C over a period of 5	•
	minutes, and the mixture was stirred at said temperature for 5 hours to deposit crystals. The deposited crystals were collected by filtration, washed two times with 4 ml of water,	30
30	further washed two times with 4 ml of isopropanol, and then dried to obtain 4.0 g of a dihydrate of $6-[D(-)-\alpha-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)$ phenylacetamido] penicillanic acid, m.p. 156—157°C (decomp.), yield 75.4%.	30
	IR (KBr) cm ⁻¹ : $\nu_{C=0}$ 1775, 1740, 1695, 1670	
35	NMR (d ₆ -DMSO) τ values: 0.18 (1H, d), 0.77 (1H, d), 2.66 (5H, s), 4.30 (1H, d), 4.40 (3H, br), 4.48 (1H, g), 4.65 (1H, d), 5.80 (1H, s), 6.12 (2H, bs), 6.45 (2H, bs), 7.06 (3H, s), 8.48 (3H, s), 8.60 (3H, s)	35
	The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-	
40	1-piperazinocarbonyl chloride was replaced by 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride, to obtain a monohydrate of $6-[D(-)-\alpha-(4-\text{ethyl-2,3-dioxo-1-piperazino-carbonylamino})$ phenylacetamido] penicillanic acid, m.p. 154—156°C (decomp.), yield	40
40	84.8%.	
	IR (KBr) cm ⁻¹ : $\nu_{c=0}$ 1775, 1735, 1705, 1680, 1665 NMR (d _e -DMSO) τ values: 0.20 (1H, d), 0.76 (1H, d), 2.69 (5H, s), 4.32	
	(1H, d), 4.53 (1H, q), 4.64 (1H, d), 5.00 (3H, br), 5.83 (1H, s), 6.13 (2H, bs), 6.49 (2H, bs), 6.62 (2H, q), 8.44 (3H, s), 8.58 (3H, s),	45
45	8.91 (3H, t)	
	The thus obtained monohydrate was neutralized with an aqueous sodium hydrogen- carbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium	=
50	salt of $6-[D(-)-\alpha-(4-\text{ethyl-}2,3-\text{dioxo-}1-\text{piperazinocarbonylamino})$ phenylacetamido]-penicillanic acid.	50
50	Further, a solution in 10 ml of nitromethane of 2 g of the aforesaid dihydrate of $6 - (D(-)) - \alpha - (4 - \text{methyl} - 2.3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	•
	amido] penicillanic acid was allowed to stand overnight to deposit crystals, which were then collected by filtration to obtain 2 g of a monohydrate of a nitromethane addition	
55	product of $6-[D(-)-\alpha-(4-\text{methyl-}2,3-\text{dioxo-}1-\text{piperazinocarbonylamino})$ phenylacetamido] penicillanic acid, m.p. 128—130°C (decomp.), yield 92.2%.	55

Elementary analysis (for C₂₂H₂₃N₃O₇S . CH₃NO₂ . H₂O): Calculated (%) C: 47.42 H: 5.19 N: 14.43 Found (%) C: 47.94 H: 5.13 N: 14.53

NMR (d _c -DMSO) γ vanies: 0.22 (1H, d _f), 0.30 (1H, d _f), 3.5 (1H, s _f), s. (3H, s _f), 8.1 (1H, s _f), 6.13 (2H, bs), 6.46 (2H, bs), 7.07 (3H, s _f), 8.45 (3H, s _f), 8.58 (3H, s _f) Example 24. To a suspension of 1.6 g of a trihydrate of D(-)-α-aminobenzyl penicillin in 20 ml of water was added at 2° to 3°C 0.54 g of potassium carbonate, and the resulting mixture was stirred for 3 minutes. To the mixture was gradually added 0.81 g of 4 ethyl-2,3-dioxo-1-piperazinocarbonyl chloride at said temperature over a period of 10 minutes, and the mixture was reacted for 15 minutes. After the reaction, slight amounts of insolubles formed were separated by filtration, and the filtrate was charged into 10 ml of methyl n-propyl ketone. Into the resulting mixture was dropped 1.98 ml of 2N HCl at 15° to 20°C over a period of 2 minutes, and the mixture was stirred at said temperature for 1 hour to deposit crystals. The deposited crystals were collected by filtration, washed two times with 2 ml of water, further washed two times with 2 ml of methyl n-propyl ketone, and then dried to obtain 1.7 g of a monohydrate of D(-)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino) benzylpenicillin, m.p. 152—154°C (decomp.), yield 80.2%. The thus obtained product was neutralized with an aqueous sodium hydrogen-carbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of the said product. Example 25. A suspension of 4.0 g of a monohydrate of 7-[D(-)-α-aminophenylacetamido]-3-methyl-2'-cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was rea		IR (KBr) cm ⁻¹ : v _{C=0} 1770, 1735, 1700, 1680	
Example 24. To a suspension of 1.6 g of a trihydrate of D(-)-\alpha-aminobenzyl penicillin in 20 ml of water was added at 2° to 3°C.0.4 g of potassium carbonate, and the resulting mixture was stirred for 3 minutes. To the mixture was gradually added 0.81 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride at said temperature over a period of 10 minutes, and the mixture was reacted for 15 minutes. After the reaction, slight amounts of insolubles formed were separated by filtration, and the filtrate was charged into 10 ml of methyl n-propyl ketone. Into the resulting mixture was dropped 1.98 ml of 2N HCl at 15° to 20°C over a period of 2 minutes, and the mixture was stored at said temperature for 1 hour to deposit crystals. The deposited crystals were collected by filtration, washed two times with 2 ml of water, further washed two times with 2 ml of methyl n-propyl ketone, and then dried to obtain 1.7 g of a monohydrate of D(-)-\alpha-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)benzylpenicillin, m.p. 152—154°C (decomp.), yield 80.2%. The thus obtained product was neutralized with an aqueous sodium hydrogen-carbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of the said product. Example 25. A suspension of 4.0 g of a monohydrate of 7-[D(-)-\alpha-aminophenylacetamido]-3-methyl-\alpha-2-cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0 After the reaction, the reaction liquid was stirred together with 60 ml of idiethyl ether a		NMR (d_0 -DMSO) τ values: 0.22 (1H, d), 0.80 (1H, d), 2.69 (5H, s), 3.30 (3H, br), 4.30 (1H, d), 4.46—4.70 (2H), 5.67 (3H, s), 5.81 (1H, s),	•
To a suspension of 1.6 g of a trihydrate of D(—)-α-aminobenzyl penicillin in 20 ml of water was added at 2° to 3°C 0.54 g of potassium carbonate, and the resulting mixture was stirred for 3 minutes. To the mixture was gradually added 0.81 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride at said temperature over a period of 10 minutes, and the mixture was reacted for 15 minutes. After the reaction, slight amounts of insolubles formed were separated by filtration, and the filtrate was charged into 10 ml of methyl n-propyl ketone. Into the resulting mixture was dropped 1.98 ml of 2h HCl at 15° to 20°C over a period of 2 minutes, and the mixture was strated at said temperature for 1 hour to deposit crystals. The deposited crystals were collected by filtration, washed two times with 2 ml of water, further washed two times with 2 ml of methyl n-propyl ketone, and then dried to obtain 1.7 g of a monohydrate of D(—)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)benzylpenicillin, m.p. 152—154°C (decomp.), yield 80.2°/c. The thus obtained product was neutralized with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of the said product. Example 25. A suspension of 4.0 g of a monohydrate of 7-[D(—)-α-aminophenylacetamido]-3-methyl-3-cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0 After the reaction, the reaction iquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the a	•	6.13 (2H, bs), 6.46 (2H, bs), 7.07 (3H, s), 8.45 (3H, s), 8.58 (3H, s)	
mixture was stirred for 3 minutes. To the mixture was gradually added 0.31 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride at said temperature over a period of 10 minutes, and the mixture was reacted for 15 minutes. After the reaction, slight amounts of insolubles formed were separated by filtration, and the filtrate was charged into 10 ml of methyl n-propyl ketone. Into the resulting mixture was dropped 1.98 ml of 2N HCl at 15° to 20°C over a period of 2 minutes, and the mixture was stirred at said temperature for 1 hour to deposit crystals. The deposited crystals were collected by filtration, washed two times with 2 ml of water, further washed two times with 2 ml of methyl n-propyl ketone, and then dried to obtain 1.7 g of a monohydrate of D(-)-\alpha-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)benzylpenicillin, m.p. 152—154°C (decomp.), yield 80.2%. The thus obtained product was neutralized with an aqueous sodium hydrogen-carbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of the said product. Example 25. A suspension of 4.0 g of a monohydrate of 7-[D(-)-\alpha-aminophenylacetamido]-3-methyl-\alpha'-cephem-4-carboxylic acid in 60 ml of tertahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the aqueous layer was separated off. The thus obtained aqueous layer was washed with 30 ml of ethyl acetare, cooled to 0° to 5°C, and then adjusted to a	. 5	To a suspension of 1.6 g of a trihydrate of $D(-)-\alpha$ -aminobenzyl penicillin in 20	5
perature for 1 hour to deposit crystals. The deposited crystals were collected by filtration, washed two times with 2 ml of water, further washed two times with 2 ml of methyl n-propyl ketone, and then dried to obtain 1.7 g of a monohydrate of D(-)-α-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)benzylpenicillin, m.p. 152—154°C (decomp.), yield 80.2%. The thus obtained product was neutralized with an aqueous sodium hydrogencarbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of the said product. Example 25. A suspension of 4.0 g of a monohydrate of 7-[D(-)-α-aminophenylacetamido]-3-methyl-λ²-cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the aqueous layer was separated off. The thus obtained aqueous layer was washed with 30 ml of ethyl acetae, cooled to 0° to 5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of 7 - [D(-) - α-(4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive deformal (III) shown in Table 21, to obtain respective objective compounds of formula (III) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each objective compound	10	mixture was stirred for 3 minutes. To the mixture was gradually added 0.81 g of 4-ethyl-2,3-dioxo-1-piperazinocarbonyl chloride at said temperature over a period of 10 minutes, and the mixture was reacted for 15 minutes. After the reaction, slight amounts of insolubles formed were separated by filtration, and the filtrate was charged into 10 ml of methyl n-propyl ketone. Into the resulting mixture was dropped 1.98 ml of 2N HCl	10
The thus obtained product was neutralized with an aqueous sodium hydrogen- carbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium salt of the said product. Example 25. A suspension of 4.0 g of a monohydrate of 7-[D()-α-aminophenylacetamido]-3- methyl-Δ³-cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the aqueous layer was separated off. The thus obtained aqueous layer was washed with 30 ml of ethyl acetate, cooled to 0° to 5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of 7 - [D(-) - α-(4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl- Δ³ - cephem - 4 - carboxylic acid, m.p. 185–186°C (decomp.), yield 86%. IR (KBr) cm ⁻¹ : ν _{C=0} 1770—1760 (lactam), 1720—1660 (—CON<, —COOH) NMR (d₀-DMSO) r values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s), 7.05 (3H, s), 8.02 (3H, s)	15	perature for 1 hour to deposit crystals. The deposited crystals were collected by filtration, washed two times with 2 ml of water, further washed two times with 2 ml of methyl n-propyl ketone, and then dried to obtain 1.7 g of a monohydrate of D(-)-\alpha-(4-ethyl-2,3-dioxo-1-piperazinocarbonylamino)benzylpenicillin, m.p. 152—154°C (decomp.) yield 80.2%	15
A suspension of 4.0 g of a monohydrate of 7-[D(-)-α-aminophenylacetamido]-3-methyl-Δ³-cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the aqueous layer was separated off. The thus obtained aqueous layer was washed with 30 ml of ethyl acetate, cooled to 0° to 5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of 7 - [D(-) - α-(4-methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl-Δ³ - cephem - 4 - carboxylic acid, m.p. 185—186°C (decomp.), yield 86%. IR (KBr) cm ⁻¹ : v _{C=0} 1770—1760 (lactam), 1720—1660 (—CON <, —COOH) NMR (d ₀ -DMSO) - values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s), 7.05 (3H, s), 8.02 (3H, s) The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxol-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (1II) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each objective compound was confirmed by IR	20	The thus obtained product was neutralized with an aqueous sodium hydrogen- carbonate solution, and then subjected to filtration and freeze-drying to obtain a sodium	20
methyl-\$\text{\alpha}\$-cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20%, by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the aqueous layer was separated off. The thus obtained aqueous layer was washed with 30 ml of ethyl acetate, cooled to 0° to 5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of 7 - [D(-) - \alpha (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - methyl-\$\text{\alpha}\$ - cephem - 4 - carboxylic acid, m.p. 185—186°C (decomp.), yield 86%. IR (KBr) cm ⁻¹ : \$\nu_{c=0}\$ 1770—1760 (lactam), 1720—1660 (—CON<, —COOH) NMR (d ₀ -DMSO) \$\tau\$-values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s), 7.05 (3H, s), 8.02 (3H, s) The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxolopounds of formula (III) shown in Table 21, to obtain respective derivatives of compounds as shown in Table 21. The structure of each objective compound was confirmed by IR		Example 25.	
maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl ether and 70 ml of water, and then the aqueous layer was separated off. The thus obtained aqueous layer was washed with 30 ml of ethyl acetate, cooled to 0° to 5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of 7 - [D(-) - α-(4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - methyl-Δ³ - cephem - 4 - carboxylic acid, m.p. 185—186°C (decomp.), yield 86%. IR (KBr) cm ⁻¹ : ν _{C=0} 1770—1760 (lactam), 1720—1660 (—CON<, —COOH) NMR (d ₀ -DMSO) τ-values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s), 7.05 (3H, s), 8.02 (3H, s) The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each objective compound was confirmed by IR	25	methyl- Δ^3 -cephem-4-carboxylic acid in 60 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by gradual addition of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution were gradually added 2.5 g of crystals of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 10 minutes. During this period, the pH of the reaction solution was	25
 5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - methyl-Δ³ - cephem - 4 - carboxylic acid, m.p. 185—186°C (decomp.), yield 86%. IR (KBr) cm⁻¹: ν_{C=0} 1770—1760 (lactam), 1720—1660 (—CON <, —COOH) NMR (d₀-DMSO) τ-values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s), 7.05 (3H, s), 8.02 (3H, s) The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each objective compound was confirmed by IR 	30	maintained at 7.5 to 8.0 by gradual addition of triethylamine. Subsequently, the resulting mixture was reacted at 0° to 5°C for 15 minutes while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the reaction liquid was stirred together with 60 ml of diethyl other and 70 ml of water, and then the aqueous layer was separated off. The	30
NMR (d ₀ -DMSO) τ -values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s), 7.05 (3H, s), 8.02 (3H, s) The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each objective compound was confirmed by IR	35	5°C, and then adjusted to a pH of 1.5 by addition of dilute hydrochloric acid to deposit white crystals. The deposited crystals were collected by filtration, sufficiently washed with water and then dried to obtain 4.7 g of white crystals of $7 - [D(-) - \alpha - (4 - \text{methyl} - 2.3 - \text{diox} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - methyl-	35
1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of com- pounds of formula (III) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each objective compound was confirmed by IR	40	NMR (d_0 -DMSO) τ -values: 0.1 (1H, d), 0.56 (1H, d), 2.62 (5H, s), 4.26—4.37 (2H, dd), 5.05 (1H, d), 6.1 (2H, bs), 6.47 (2H, bs), 6.63 (2H, s),	40
	45	1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 21, to obtain respective objective compounds as shown in Table 21. The structure of each objective compound was confirmed by IR	45

Table 21

Reactive derivative of compound of formula (III)	Objective compound
ооо сн ₃ сн ₂ -и и-сос1	$D(-)- OOO CH_2CH_2 - NOON - CONHCHCONH - SOOO COOOH$ $D OOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOOO$
CH3CH2-N N-COC1	D(-)- CH ₃ CH ₂ CH ₂ -N N-CONHCHCONH S CH ₃ CH ₂ CH ₂ O COOH m.p. (decomp.) 160°C, yield 80.5 %
сн ₃ (сн ₂) ₂ сн ₂ -м м-сос1	CH ₂ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH S O CH ₃ COOH m.p. (decomp.) 150°C, yield 76 %

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Example 26.

(1) To a solution of 0.92 g of 1-n-pentyl-2,3-dioxo-piperazine in 15 ml of anhydrous dioxane were added 1.1 ml of triethylamine and 1.08 g of trimethylsilyl chloride. The resulting mixture was stirred at room temperature for 20 hours to form triethylamine hydrochloride. This hydrochloride was separated by filtration, and the filtrate was dropped at 0° to 5°C into a solution of 0.6 g of phosgene in 10 ml of anhydrous tetrahydrofuran. Subsequently, the resulting mixture was reacted at 5° to 10°C for 30 minutes and then at room temperature for 2 hours. Thereafter, the solvent was removed by distillation under reduced pressure to obtain 1.21 g of pale yellow, oily 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride.

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IR (film) cm⁻¹: $\nu_{C=0}$ 1790, 1720—1665

(2) A suspension of 1.70 g of a monohydrate of 7-[D(-)- α -aminophenylacetamido]-3-methyl-A3-cephem-4-carboxylic acid in 50 ml of tetrahydrofuran containing 20% by volume of water was adjusted to a pH of 8.0 to 8.5 by addition of triethylamine with stirring to form a solution. This solution was cooled to 0° to 5°C, and 7 ml of an anhydrous tetrahydrofuran solution containing 1.21 g of the 4-n-pentyl-2,3-dioxo-1piperazinocarbonyl chloride obtained in (1) was dropped into the solution. During this period, the pH of the solution was maintained at a pH of 7.5 to 8.0 by addition of triethylamine. Subsequently, the resulting mixed solution was reacted at 0° to 5°C for 1 hour and then at 5° to 10°C for 2 hours while maintaining the pH thereof at 7.5 to 8.0. After the reaction, the tetrahydrofuran was removed by distillation under reduced pressure, and the residue was dissolved in 20 ml of water and then washed two times with 20 ml of ethyl acetate. The aqueous layer was again charged with 40 ml of ethyl acetate, and then adjusted to a pH of 1.5 by gradual addition of dilute hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, washed with water, and then dried over anhydrous magnesium sulfate. Thereafter, 10 ml of an ethyl acetate solution containing 0.75 g of sodium 2-ethylhexanoate was dropped into the layer at 0° to 5°C to deposit white crystals. The deposited crystals were collected by filtration, and washed with ethyl acetate and then with diethyl ether to obtain 1.95 g of a sodium salt of $7 - [D(-) - \alpha - (4 - n - pentyl - 2,3 - dioxo - 1 - piper-azinocarbonylamino) phenylacetamido] - 3 - methyl - <math>\Delta^3$ - cephem - 4 - carboxylic acid, m.p. 164—166°C (decomp.), yield 75%.

IR (KBr) cm⁻¹: $\nu_{0=0}$ 1750 (lactam), 1720—1660 (—CON<), 1590 (—COO \ominus) NMR (d₈-DMSO|+ D₂O) τ values: 2.58 (5H, s), 4.33 (1H, s), 4.49 (1H, d), 5.17 (1H, d), 6.10 (2H, bs), 6.42—6.87 (6H, m), 8.09 (3H, s), 8.60—8.90 (6H, bs), 9.12 (3H, t)

The above-mentioned operation was repeated, except that the 4-n-pentyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 22, to obtain respective objective compounds as shown in Table 22. The structure of each objective compound was confirmed by IR and NMR.

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Table 2

Objective compound	D(-)- CH ₂ (CH ₂) ₄ CH ₂ -M N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -M N-CONHCHCONH CH ₃ CH ₃ CH ₃ CH ₂ (CH ₂) ₄ CH ₂ -M N-CONHCHCONH CH ₃ CH ₂ CH ₃	$D(-)-$ $CH_{3}(CH_{2})_{5}CH_{2}-N$ O O $CH_{3}(CH_{2})_{5}CH_{2}-N$ O	D(-)- $CH_{2}(CH_{2})_{6}CH_{2}-M$ $CH_{3}(CH_{2})_{6}CH_{2}-M$ $CH_{4}(CH_{2})_{6}CH_{2}-M$ $CH_{4}(C$
Reactive derivative of compound of formula (III)	ооо сн ₃ (сн ₂) ₄ сн ₂ -и м-сосэ	сн ₃ (сн ₂) ₅ сн ₂ -м м-сос1	сн ₃ (сн ₂) ₆ сн ₂ -и и-сос1

cont'd

Table 22 (Cont'd)

CH ₃ CH ₂ OCO-N N-COC1	CH ₂ CH ₂ OCO-N N-CONHCHCONH S CH ₂ CH ₃ CH ₂ OCO-N O-CONHCHCONH CH ₃ O-COONA m.p. (decomp.) 185 - 188°C, yield 77 %
он ₃ (сн ₂) ₄ сн ₂ -м м-сосл	D(-)- CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH CH ₃ CH ₃ CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₂) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₂ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₄ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₄ -N N-CONHCHCONH S CH ₃ (CH ₃) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₃) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₃) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S CH ₄ (CH ₄) ₄ CH ₄ -N N-CONHCHCONH S

Example 27. Using 1.5 g of a hydrochloride of methoxymethyl ester of $7-[D(-)-\alpha-amino$ phenylacetamido]-3-methyl-2,3-cephem-4-carboxylic acid and 0.65 g of 4-methyl-2,3dioxo-1-piperazinocarbonyl chloride, the same operation as in Example 25 was repeated to obtain 1.6 g of a methoxymethyl ester of $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) phenylacetamido] - 3 - \text{methyl} - \Delta^3 - \text{cephem} - 4 - \text{carboxylic acid, m.p. } 146—148°C (\text{decomp.}), yield 86%.$ 5 5 IR (KBr) cm⁻¹: $\nu_{0=0}$ 1770 (lactem), 1710 (ester), 1680—1600 (—CON<) Example 28. To a suspension of 0.20 g of 7- $[\hat{D}(-)-\alpha$ -aminophenylacetamido]-3-acetoxy-10 10 methyl-A⁶-cephem-4-carboxylic acid in 15 ml of anhydrous chloroform was added 0.17 ml of triethylamine with stirring to form a solution, which was then cooled to 0°C. To this solution was added 0.11 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride, and the resulting mixture was reacted at room temperature for 2 hours. After the reac-15 15 tion, the reaction liquid was evaporated under reduced pressure, and the residue was dissolved in 15 ml of water. The resulting solution was washed with 10 ml of ethyl acetate. The aqueous layer was again charged with 20 ml of ethyl acetate, and then adjusted to a pH of 1.5 by addition of 2N hydrochloric acid with ice-cooling. Subsequently, the ethyl acetate layer was separated off, successively washed with water and a saturated aqueous sodium chloride solution, and then dried over magnesium sulfate. 20 20 Thereafter, the solvent was removed by distillation under reduced pressure to obtain 0.22 g of white crystals of $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{diox}o - 1 - \text{piper-azinocarbonylamino}) phenylacetamido] - 3 - acetoxymethyl - <math>\Delta^3$ - cephem - 4 - carboxylic acid, m.p. 175°C (decomp.), yield 76%. 25 IR (KBr) cm⁻¹: $\nu_{C=0}$ 1770 (lactam), 1720—1650 (—CON<, —COOH) NMR (d₆-DMSO) τ values: 0.23 (1H, d), 0.63 (1H, d), 2.66 (5H, s), 4.32 (1H, q), 4.43 (1H, d), 5.05 (1H, d), 5.21 (2H, q), 6.15 (2H, bs), 6.40 (2H, bs), 6.57 (2H, bs), 7.0 (3H, s), 8.0 (3H, s) 25 The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-30 30

The above-mentioned operation was repeated, except that the 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride was replaced by each of the reactive derivatives of compounds of formula (III) shown in Table 23, to obtain respective objective compounds as shown in Table 23. The structure of each objective compound was confirmed by IR and NMR.

Table 23

Objective compound	D(-)- CH ₃ CH ₂ -N N-CONHCHCONH S CH ₂ CH ₂ -N N-CONHCHCONH CH ₂ COCH ₃ COOH m.p. (decomp.) 150°C, yield 83.4 %	D(-)- CH ₃ CH ₂ -N N-CONHCHCONH S CH ₂ OCOCH ₃ O COOH m.p. (decomp.) 165°C, yield 83 %	$D(-) CH_3)_2CH-M$ $M-CONHCHCONH$ $CH_3)_2CH-M$ CH_2OCOCH_3 CH_3OCOCH_3 CH_3OCOCH_3 CH_3OCOCH_3 CH_3OCOCH_3 CH_3OCOCH_3 CH_3OCOCH_3 CH_3OCOCH_3 CH_3OCOCH_3 CH_3OCOCH_3
Reactive derivative of compound of formula (III)	CH ₂ CH ₂ CH ₂ -N N-COCL	о о о с сн ₃ сн ₂ -и м-сос1	СН ₃)2СН-М М-СОС1

Cont.1d

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Table 23 (Cont'd)

CH3CH2-N N-CSC1	D(-)- 0 0 CH ₂ CH ₂ -N N-CSNHCHCONH S CH ₂ OCOCH ₃ O 0 COOH m.p. (decomp.) 112°C, yield 95 %
CH3-N-CSC1	D(-)- CH ₃ -N N-CSNHCHCONH S CH ₂ OCOCH ₃ O COOH m.p. (decomp.) 134°C, yield 90.2 %

The aforesaid $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazino-}$ carbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, m.p. 175°C (decomp.), was recrystallized from hydrous acetone to obtain white crystals showing a melting point of 198° to 200°C (decomp.).

15. 2 Example 29.

(1) To a solution of 28.2 g of a sodium salt of D(—)-phenylglycine in 150 ml of water were added 200 ml of ethyl acctate and 18.2 g of triethylamine, and the resulting mixture was cooled to 0°C. To this mixture was added 34.3 g of 4-methyl-2,3-dioxo-1-piperazinocarbonyl chloride over a period of 15 minutes, and the mixture was reacted at 5° to 10°C for 15 minutes. Thereafter, the aqueous layer was separated off and adjusted to a pH of 0.5 by addition of 2N hydrochloric acid with ice-cooling to deposit crystals. The deposited crystals were collected by filtration and then dried to obtain 42 g of white crystals of D(—)-α-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid. 2 15

D(-)-a-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid obtained in the above-mentioned item (1) was added 0.11 g of N-methylmorpholine with stirring to form a solution, which was then cooled to -20°C. To this solution was added 3 ml of an anhydrous methylene chloride solution containing 0.13 g of ethyl chlorocarbonate, and the resulting mixture was reacted at -10°C to -20°C for 60 minutes

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5	to form a mixed acid anhydride. Into the thus formed acid anhydride was dropped a solution formed by adding 0.50 ml of triethylamine to a suspension in 5 ml of methanol of 0.41 g of 7 - amino - 3 - $[2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl}) - \text{thiomethyl}] - \Delta^3$ - cephem - 4 - carboxylic acid. After the dropping, the resulting mixture was reacted at -50° to -30°C for 30 minutes, at -30° to -20°C for 30 minutes, at -20° to 0°C for 60 minutes, and then at room temperature for 30 minutes. Thereafter, the reaction liquid was concentrated under reduced pressure, and the concentrate was dissolved	5
10	in 10 ml of water, washed with 5 ml of ethyl acetate, again charged with 15 ml of ethyl acetate, and then adjusted to a pH of 1.5 by addition of 2N hydrochloric acid with ice-cooling. Subsequently, insolubles were separated by filtration, and the ethyl acetate layer was separated off, successively washed with water and a saturated sodium chloride solution, dried over magnesium sulfate, and then freed from the solvent by distillation	10
15	under reduced pressure to obtain 0.58 g of pale yellow crystals of $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}] - 3 - [2-(5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4 - carboxylic acid, m.p. 160°C (decomp.), yield 91%.$	15
20	IR (KBr) cm ⁻¹ : $\nu_{0=0}$ 1780 (lactam), 1650—1720 (—CON<, —COOH) NMR (d ₀ -DMSO) τ values: 0.2 (1H, d), 0.6 (1H, d), 2.60 (5H, s), 4.35 (1H, q), 4.40 (1H, d), 5.0 (1H, d), 5.70 (2H, q), 6.10 (2H, bs), 6.25—6.55 (2H, 2H, bs), 7.0 (3H, s), 7.30 (3H, s)	20
- 25	The above-mentioned operation was repeated, except that the $D(-)-\alpha$ -(4-methvl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 24, to obtain respective objective compounds as shown in Table 24. The structure of each objective compound was confirmed by IR and NMR.	25

Table 24

Compound of formula (V)	Objective compound
D(-)- 0 0 с сн ₂ сн ₂ -и м-сомненсоон	D(-)- 0 0 CH3CH2-N N-CONHCHCONH S CH2S N-N CH2S S CH3 CH2S S CH2S CH2
D(-)- CH ₃ CH ₂ CH ₂ -N N-соинсисоон	D(-)- CH ₃ CH ₂ CH ₂ -N CH ₃ -N CH ₃ CH ₂ -N CH ₃ CH ₃ -N CH
D(-)- CH ₂ (CH ₂) ₂ CH ₂ -N -CONHCHCOOH	D(-)- CH ₂ (CH ₂) ₂ CH ₂ -M N-CONHCHCONH S N-N CH ₂ S N-N CH ₃ O COOH m.p. (decomp.) 144°C, yield 84.3 %

(Cont'd) Table 24

D(-)-	O-N N-CONHCHCONH S CH28 N-N CH28 CH3	m.p. (decomp.) 167°C, yield 93 %
D(-)-	(○)-и _v-conнснсоон (○)	

2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methy 1,2,3,4 - tetrazolyl) - thiomethyl] - \(\Lambda \) - cephem - 4 - carboxylic acid, m.p. 161 163 \(\text{Gecomp.} \), yield 76%. amino) phenylacetic acid and 0.33 g of 7 - amino - 3 - [5 - (terrazolyl) - thiomethyl] - \(\text{\alpha}_3 \) - cephen - 4 - carboxylic acid, the in Example 29 was repeated, to obtain 0.5 g of 7 - [D(-Using 0.3 g of D(-) S

2 IR (nujol) cm⁻¹: v₀₌₀ 1775 (lactam), 1720—1660 (—CON<, —COOH)
NMR (d₆-DMSO) τ values: 0.02 (1H, d), 0.34 (1H, d), 2.48 (5H, s), 4.17
(1H, q), 4.26 (1H, d), 4.92 (1H, d), 5.66 (2H, s), 6.01 (5H, s), 6.35
(4H, s), 7.0 (3H, s) 15 10

The above-mentioned operation was repeated, except that the D(-)- α -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 25, to obtain respective objective compounds as shown in Table 25. The structure of each objective compound was confirmed by IR and NMR.

Table 25

Compound of formula (V)	Objective compound
D(-)-	D(-)-
CH2-N N-CONHCHCOOH	CH ₂ CH ₂ -N N-CONHCHCONH S N-N
CH ₂	* CH2 O O COOH *
	m.p. (decomp.) 170°C, yield 63.6 %
ρ(-)σ	o -(-)a
снз-и и-соинснооон	CH3-N-CONHCHCONH-S-N-N
(a)	CH2 COOH CH2
	m.p. (десоmp.) 173°С, yield 68 % ~3
D(-)-	D(-)-
О при-сомненсоон	N-N S N-N
©	NAC BOOD O O
	m.p. (decomp.) 163°C, yield 74.8 %

Anhydrous methylene chloride was substituted for the methanol used in Example 29.

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Exam	nle	31.

Using 0.30 g of D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid and 0.34 g of 7 - amino - 3 - [5 - (1,3,4 - thiadiazolyl)-thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, the same operation as in Example 29 was repeated, to obtain 0.47 g of 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1-piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, m.p. 158—159°C (decomp.), yield 71.5°/

IR (nujol) cm⁻¹: $\nu_{G=0}$ 1775 (lactam), 1720—1660 (—CON<, —COOH)

The above-mentioned operation was repeated, except that the D(-) - α
(4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid was replaced by D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)
phenylacetic acid, to obtain 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl]
Δ³ - cephem - 4 - carboxylic acid, m.p. 123°C (decomp.), yield 64.5%.

Example 32.

Using 0.31 g of D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetic acid and 0.39 g of 7 - amino - 3 - [2 - (1 - methyl - 1,3,4-triazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, the same operation as in Example 29 was repeated, except that the methanol was replaced by anhydrous methylene chloride, to obtain 0.43 g of 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1-piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl)-thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid, yield 70%.

IR (Nujol) cm⁻¹: $\nu_{0=0}$ 1780 (lactam), 1720—1650 (—CON<, —COOH)

The above-mentioned operation was repeated, except that the $D(-)-\alpha$ -(4-methyl-2,3-dioxo-1-piperazinocarbonylamino)phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 26, to obtain respective objective compounds as shown in Table 26. The structure of each objective compound was confirmed by IR and NMR.

Table 26

Compound of formula (V)	Objective compound
D(-)-	D(-)-
CH ₂ CH ₂ -N -CONECHCOOE	CH ₂ CH ₂ -N N-CONHCHCONH CH ₂ S N-N
	CH ₂ m.p. (decomp.) 147°C, yield 68.5 %
D(-)-	D(-)-
о о о	O-N-N-CONHCHCONH-LS N-N
(i)	СООН СИЗ m.p. (decomp.) 158 ⁰ C, yield 74.5 %

Example 33.

The procedure of Example 29 was repeated, except that the D(—)-\(\alpha\)-(4-methyl-2,3-dioxo-1-piperazinocarbonylamino) phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 27, to obtain respective objective compounds shown in Table 27. The structure of each objective compound was confirmed by IR and NMR.

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Table 27

Compound of formula (V)	Objective compound
D(-)-	D(-)-
сн ₃ со-и м-сомеснсоон	CH ₂ CO-N N-CONHCHCONH S N-N CH ₂ CO-N CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CO-N COOH
D(-)-	D(-)-
сн ₃ 802-и й-соинснсоон	CH ₂ SO ₂ -N N-CONHCHCONH S N-N CH ₂ S L S CH ₃ CH ₃
D(-)-	D(-)-
сн ₃ -и й-сомнснсоон	CH ₃ -N N-CONHCHCONH S N-N CH ₂ CH ₃

Table 27 (Cont'd)

D(-)-	D(-)-
сн ₃ сн ₂ -и й-соинснсоон	CH ₂ CH ₂ -N N-CONHCHCONH S N-N CH ₂ S L CH ₃ CH ₃
D(-)-	D(-)-
CH3CONHCO-N N-CONHCHCOOH	CH ₂ CONHCO-N N-CONHCHCONH S CH ₂ S-L _S CH ₃
D(-)-	D(-)-
сн ₅ -и м-сомнснсоон	CH3-N N-CONHCHCONH N CH2S US US CH3

Table 27 (Cont'd)

D(-)-	D(-)-
сн ₃ сн ₂ -и м-соинснсоон	CH ₂ CH ₂ -N N-CONHCHCONH S N-N CH ₂ S S CH ₃ CH ₃
D(-)-	D(-)-
ни и-сомненсоон	HN N-CONHCHCONH S OH S LIST CH2
D(-)-	D(-)-
сн ₃ со-и и-соинснсоон	CH ₂ CO-N N-CONHCHCONH S N-N CH ₂ N-N CH ₂ CH

Example 34.

The procedure of Example 30 was repeated, except that the D(-)-\(\sigma\)-(4-methyl-2,3-\(\delta\)-ioxo-1-piperazinocarbonylamino) phenylacetic acid was replaced by each of the compounds of formula (V) shown in Table 28, to obtain respective objective compounds shown in Table 28. The structure of each objective compound was confirmed by IR and NMR.

Table 28

D(-)-D(-)-D(-)-D(-)-D(-)-D(-)-D(-)-D(-)

cont'd.

Table 28 (Cont'd)

D(-)-	D(-)-
CH ₂ CH ₂ -N N-CONHCHCOOH	CH ₂ CH ₂ -N N-CONHCHCONH S N-N CH ₂ S N-N N-N CH ₂ S N-N N-N CH ₂ S N-N N-N N-N N-N N-N N-N N-N N-N N-N N-
D(-)-	D(-)-
сн ₃ соинсо-и л-соинсьсоон	CH ₃ CONHCO-N N-CONHCHCONH S N-N N-N CH ₂ S N-N N-N O COOH CH ₃ N-N CH ₃ N
D(-)d	D(-)-
сн3-и м-соинсисоон	CH3-NN-CONFICHCONH S N-N N-N CH2S-UNN O COOH CH3

- cont'd -

Table 28 (Cont'd)

D(-)- сн ₃ сн ₂ -м м-сомнснсоон	D(-)-CONHCHCONH
D(-)- о о о о о о о	D(-)- O HN N-CONHCHCONH O COOH CH2 CH3
D(-)- сн ₃ со-и 0 Сн ₃ со-и 0 О	$D(-)-$ $CH_{5}CO-N$ O

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1,508,062 147 Example 35. (1) To a suspension of 0.9 g of D(-)- α -alanine in 15 ml of water was added 2.05 g of triethylamine to dissolve D(-)- α -alanine in water, and the resulting solution was cooled to 0°C. To the solution was added 2.3 g of 4-methyl-2,3-dioxo-1-piperazino-5 carbonyl chloride over 15 minutes, after which reaction was effected for 30 minutes with ice-cooling. Dilute hydrochloric acid was then added to the reaction product to adjust the pH thereof to 2.0. The water was removed by distillation under reduced pressure. and 30 ml of acetone was added to the residue, after which insolubles were filtered off. To the resulting acetone solution was added 10 ml of an acetone solution 10 of 1.6 g of a sodium salt of 2-ethylhexanoic acid, and the deposited crystals were collected by filtration, and dried to obtain 2.1 g of a sodium salt of $D(-)-\alpha-(4-methyl-$ 2,3-dioxo-1-piperazinocarbonylamino) propionic acid having a melting point of 115— 8°C (decomp), yield 78.5%. IR (KBr) cm⁻¹: $\nu_{C=0}$ 1700, 1680, 1600 (—CON<, —COO \ominus) (2) In the same manner as in Example 32, $7 - [D(-) - \alpha - (4 - \text{methyl-} 2,3 - \text{diox}o - 1 - \text{piperazinocarbonylamino}) \text{propionamido}] - 3 - \text{acetoxymethyl} - <math>\Delta^8$ -cephem - 4 - carboxylic acid was obtained from a sodium salt of $D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{diox}o - 1 - \text{piperazinocarbonylamino}) \text{propionic acid and } 7 - \text{amino} - 3 - \text{acetoxymethyl} - <math>\Delta^3$ - cephem - 4 - carboxylic acid. The thus obtained product was dissolved in 20 ml of acetone, and a solution of 0.65 g of a sodium salt of 2-ethylhexanoic acid in 5 ml of acetone was added to the resulting solution. The denosited crystals 15 noic acid in 5 ml of acetone was added to the resulting solution. The deposited crystals were collected by filtration and dried to obtain 1.2 g of sodium salt of $\hat{7}$ - [D(-) - α -(4 - methyl - 2,3 - dioxo - piperazinocarbonylamino)propionamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid having a melting point of 195°C 25 (decomp.), yield 67.7%. IR (KBr) cm⁻¹: $\nu_{0=0}$ 1780 (lactam), 1710—1660 (—CON<), 1600 (—COO \ominus) Example 36. In the same manner as in Example 32, $7 - [D(-) - \alpha - (4 - methyl - 2)]$ dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - [5 - (1-methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid was obtained from 7 - amino - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]-30 30 Δ^{3} - cephem - 4 - carboxylic acid and D(-) - α - (4 - methyl - 2,3 - dioxo - 1piperazinocarbonylamino) - p - hydroxyphenylacetic acid. Melting point (decomp.), 147—9°C; yield, 62.0%. 35 IR (KBr) cm⁻¹: $\nu_{C=0}$ 1765 (lactam), 1720—1660 (—CON<, —COOH) 35 Example 37. In the same manner as in Example 29, $7 - [D(-) - \alpha - (4 - methyl - 2,3$ dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - azidomethyl - Δ^a - cephem-4 - carboxylic acid was obtained from D(-) - α - (4 - methyl - 2,3 - dioxo - 1-piperazinocarbonylamino)phenylacetic acid and 7 - amino - 3 - azidomethyl - Δ^{8} -40 40 cephem - 4 - carboxylic acid. Melting point (decomp.), 185-8°C; yield, 68.0%. IR (KBr) cm⁻¹: $\nu_{\text{O=0}}$ 1775 (lactam), 1720—1660 (—CON<, —COOH) ν_{N_3} 2090 Example 38. 45 - 45 In 10 ml of a phosphoric acid buffer solution of a pH of 6.3 was suspended 0.57 g of 7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, and 0.07 g of

sodium hydrogencarbonate was dissolved therein. To the solution was then added 0.12 g of 1-methyl-5-mercapto-1,2,3,4-tetrazole to dissolve the latter in the former, and the solution was subjected to reaction for 24 hours while maintaining the pH of the solution at 6.5—6.7 by using dilute hydrochloric acid and sodium hydrogencarbonate. After the reaction, the reaction liquid was cooled, and then adjusted to a pH of 5.0 by adding dilute hydrochloric acid. The reaction liquid was sufficiently washed with ethyl acetate, after which the aqueous layer was separated off and then adjusted to a pH of 1.5 by adding dilute hydrochloric acid thereto. The deposited crystals were collected by filtration and dried, after which the dried crystals were washed with ethyl acetate to obtain

0.40 g of $7 - [D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{diox} - 1 - \text{piperazinocarbonylamino})$

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phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl)thiomethyl] - Δ^3 -cephem - 4 - carboxylic acid, m.p. 163—165°C (decomp.), yield 74.5%.

IR (KBr) cm⁻¹: $\nu_{C=0}$ 1775 (lactam), 1720—1660 (—CON<, —COOH) NMR (d_e-DMSO) τ values: 0.18 (1H, d), 0.55 (1H, d), 2.64 (5H, s), 4.3 (1H, q), 4.4 (1H, d), 5.0 (1H, d), 5.75 (2H, s), 6.05 (5H, s), 6.3—6.8 (6H), 8.92 (3H, t)

In the same manner as above, the objective compounds shown in Table 29 were obtained from 7 - $[D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl})$ -phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid or 7- $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid and the compounds of formula (VII) shown in Table 29. All the objective compounds were D(-) isomers, and the structure of each objective compound was confirmed by IR and NMR.

Table 29

Objective compound	CH3-N N-CONHCHCONH S N-N CH3-N N-CONHCHCONH CH2S UN N CH3 N-D. (decomp.) 168 - 170°C, yield 83 %	CH ₂ CH ₂ -N N-CONHCHCONH S N-N CH ₂ S S CH ₂ OCH ₂ (a) 0 COOH m.p. (decomp.) 150°C, yield 73.4 %	CH3-N N-CONHCHCONH S N-N CH2S S N
Compound of formula (VII)	N—N II N~N SH CH ₃	CH ^N SH	N—N S HS

cont'd -

Table 29 (Cont'd)

	·	
CH ₂ -N N-CONHCHCONH S CH ₂ S N-N (CH ₂ -N CH ₂ S N-N CH ₂ S N-N (O) 0 COOH H	CH ₂ -N N-CONHCHCONH S N-N CH ₂ S	CH ₂ CH ₂ -N N-CONHCHCONH S CH ₂ S N-N N-N CH ₂ S N-N N N N N N N N N N N N N N N N N N
N—N 	N N N N N N N N N N N N N N N N N N N	N—N II N—N H

cont.a -

Table 29 (Cont'd)

cont'd -

Table 29 (Cont'd)

CH ₂ N SH	CH ₃ -N N-CONHCHCONH S CH ₂ S N CH ₂ S
i ò	m.p. (decomp.) 156 - 157°C, yield 67.0 %
ES (N	CH ₂ CH ₂ -N - CONHCHCONH S CH ₂ S (Q)
→0	0 m.p. (decomp.) 177 - 180°C, yield 70.3 %
Z=	CH3-N N-CONHCHCONH S CH2S N
HS (S	m.p. (decomp.) 180 - 182°С, yield 68.7 %

- cont'd -

Table 29 (Cont'd)

CH ₃ N N SH	CH ₃ -N N-CONHCHCONH S CH ₂ S N CH ₃ -N CH ₂ S N CH ₃
HS (O)	CH ₃ -N N-CONHCHCONH S CH ₂ S (N) (decomp.) 192 - 194°C, yield 72.3 %
CH ₂ \leftarrow SH	CH ₃ CH ₂ -N N-CONHCHCONH S N-N CH ₂ S CO CH ₃ O COOH m.p. (decomp.) 175 - 178°C, yield 63.0 %

- cont'd -

Table 29 (Cont'd)

NeN3	CH ₃ -N N-CONHCHCONH S CH ₂ N ₃ CH ₃ -N N-CONHCHCONH CH ₂ -N N-CONHCHCONH CH ₃ -N N-CONHCHCONH CH ₄ -N N-
CH3-NN-C-SNa	CH ₃ -N N-CONHCHCONH S CH ₂ SC-N N-CH ₃ COOH S COO
CH ₃ N-0 " N-0 "	CH ₃ -N N-CONHCHCONH S CH ₂ SC (H ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃ COOH O CH ₂ CH ₂ CH ₂ CH ₃ COOH O CH ₂ CH ₂ CH ₃ COOH O CH ₂ CH ₂ CH ₃

3 0 1100

Table 29 (Cont'd)

	·
CH3-N - CONHCHCONH - S CH2SCOCH2CH3	m.p. (decomp.) 181 - 185°C, yield 64.3 %
CH ₂ CH ₂ OC-SNa	a

In 10 ml of water was suspended 1.15 g of 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - acetoxymethyl - Λ⁰-cephem - 4 - carboxylic acid, and 0.17 g of sodium hydrogencarbonate was then dissolved therein, after which 0.48 g of pyridine and 4.1 g of potassium thiocyanate were added thereto. The resulting mixture was subjected to reaction at 60°C for 5 hours while maintaining the pH of the mixture at 6.0 to 6.5 by adding dilute hydrochloric acid or sodium hydrogencarbonate. After the reaction, 20 ml of water was added to dilute the reaction mixture, which was then sufficiently washed with chloroform. The aqueous layer was then separated off and then adjusted to a pH of 1.5 by adding dilute hydrochloric acid. The deposited crystals were collected by filtration, dried, and then washed with acetone to obtain 1.04 g (yield, 79.6%) of a thiocyanic acid salt of 7-[D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - pyridinomethyl - Δ⁰ - cephem - 4 - carboxylic acid betaine having a melting point (decomp.) of 155—160°C, said product having the formula,

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IR (KBr) cm⁻¹: v₀₌₀ 1780 (lactam), 1720—1660 (—CON<) vSCN 2040

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In the same manner as above, a thiocyanic acid salt of $7 - [D(-) - \alpha - (4$ methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - pyridinomethyl - Δ^3 - cephem - 4 - carboxylic acid betaine was obtained from 7 - [D(-)- α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3acetoxymethyl - A^a - cephem - 4 - carboxylic acid and pyridine, said product having

Melting point (decomp.), 180—185°C; yield, 82.0%.

In a conventional manner, the above two products were treated with an ion exchange resin to obtain the desired $7 - [D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}] - 3 - pyridinomethyl - <math>\Delta^3$ - cephem - 4-carboxylic acid betaine and $7 - [D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}] - 3 - pyridinomethyl - <math>\Delta^3$ - cephem - 4 - carboxylic acid betains boxylic acid betaine.

Example 40.

In 85 ml of anhydrous methanol was dissolved 1.5 g of a sodium salt of 7- $[D(-)-\alpha-(4-\text{ethyl}-2,3-\text{dioxo}-1-\text{piperazinocarbonylamino})$ phenylacetamido]-3-[2-(pyridyl-1-oxide)thiomethyl]- Δ^3 -cephem-4-carboxylic acid. To the resulting solution was added 0.65 g of anhydrous cupric chloride, and the resulting mixture was stirred at room temperature for 15 minutes and then subjected to reaction at 50°C for 14 hours. After the reaction, hydrogen sulfide gas was passed through the reaction solution with ice-cooling for 20 minutes. The resulting insolubles were filtered off, and the filtrate was concentrated under reduced pressure. To the residue was added 20 ml of a 5% aqueous sodium hydrogencarbonate solution, and the insolubles were filtered off, after which dilute hydrochloric acid was added to the filtrate to adjust the pH to 6.5. The filtrate was then washed with 10-ml portions of ethyl acetate three times, after which the aqueous layer was separated off and then adjusted to a pH of 1.8 by adding dilute hydrochloric acid thereto. The thus deposited crystals were collected by filtration and then dried under reduced pressure and washed with 20 ml of an ethyl acetate-chloroform mixed solvent (1:1 by volume) to obtain 0.40 g of 7- $[D(-)-\alpha-(4-\text{ethyl}-2,3-\text{dioxo}-1-\text{piperazinocarbonylamino})$ phenylacetamido]-3 - methoxymethyl - Δ3 - cephem - 4 - carboxylic acid, m.p. 162-6°C (decomp.), yield 30.5%.

IR (KBr) cm⁻¹: $\nu_{G=0}$ 1770 (lactam), 1700 (—COOH), 1666 (—CON<) NMR (d_e-DMSO) τ values: 0.13 (1H, d), 0.53 (1H, d), 2.61 (5H, s), 4.31 (1H, q), 4.41 (1H, d), 4.96 (1H, d), 5.82 (2H, s), 6.10 (2H, bs), 6.33 (2H, 2H, 2H, bs), 6.79 (3H, s), 8.89 (3H, t)

The word 'Nujol' used herein is a Registered Trade Mark.

WHAT WE CLAIM IS:-1. A compound represented by the general formula (I),

> A-N3 N-C-NH-R-CONH (1)

wherein R represents an amino acid residue; R1 represents a hydrogen atom, an esterforming group capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions, an ester-forming group capable of being easily removed by mammalian enzymic action, a silicon-phosphorus- or tin-containing group which is capable of being easily removed by treatment with H₂O or an alcohol, or a conven-

tional salt-forming cation; n represents 1 or 2; nX's, which may be the same or different, represent individually an oxygen or sulfur atom, and are linked in any combination at the 2-, 3- and 5- positions of the piperazine ring; m represents 4-n; each pair of R² and R³ in linked to the same carbon atom, and m pairs of R² and R³, which may be the same or different, represent individually a hydrogen atom, a halogen atom, a carboxyl group or an unsubstituted or substituted alkyl, cycloalkyl, aryl, acyl, aralkyl, alkoxycarbonylalkyl, acyloxycarbonyl, alkoxycarbonyl, cycloalkyloxycarbonyl, aralkoxycarbonyl, aryloxycarbonyl, amino or carbamoyl group, any pair of R² and R³ together with a common carbon atom may form a cycloalkyl ring; A represents a hydrogen atom, a hydroxy group, a nitro group, a cyano group, or an unsubstituted or substituted alkyl, alkenyl, alkynyl, alkadienyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, acyl, aralkyl, acyloxycarbonyl, alkoxy, cycloalkyloxy, aryloxy, alkoxycarbonyl, cycloalkyloxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonylcarbamoyl, alkylsulfonyl, acylcarbamoyl, arylsulfonylcarbamoyl, alkylsulfonylthiocarbamoyl, arylsulfonylcarbamoyl, alkylsulfonylthiocarbamoyl, alkoxycarbonyl, alkoxycarbonylthioalkyl, alkoxythiocarbonylthioalkyl, amino or heterocyclic group; Y represents an oxygen or sulfur atom, and

where R⁴ represents a hydrogen atom, a hydroxy group, a cyano group, an azido group, a quaternary ammonium group, or an unsubstituted or substituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, thiocarbamoylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, cycloalkyloxythiocarbonylthio, amidinothio or heterocyclylthio group.

2. A compound according to claim 1, wherein R is a group represented by the formula,

wherein R⁵ represents a substituted or unsubstituted alkyl, cycloalkyl, cycloalkenyl, cycloalkadienyl, aryl, aralkyl, aryloxy, alkylthioalkyl, or heterocyclic group; and R⁵ represents a hydrogen atom; or R⁵ and R⁶ together with a common carbon atom may form a cycloalkyl, cycloalkenyl or cycloalkadienyl ring.

3. A compound according to any one of claims 1 and 2, wherein

4. A compound according to any one of claims 1 and 2, wherein

where R⁴ is as defined in claim 1.
5. A compound represented by the general formula (Ia),

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$$A - N \longrightarrow N - CO - NH - CH - CONH \longrightarrow Z$$

$$(Ia)$$

$$(R^2 R^3)_3$$

$$COOR^1$$

wherein R1, R2, R3, A and

are as defined in Claim 1 and R⁵ is as defined in Claim 2.
6. A compound represented by the general formula (Ib),

. (16)

wherein R1, R2, R3, A and

)2

are as defined in Claim 1 and R⁵ is as defined in Claim 2.
7. A compound represented by the general formula (Ic),

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wherein R1, R2, R3, A and

Z

are as defined in Claim 1 and R⁵ is as defined in Claim 2. 8. A compound represented by the general formula (Id),

15

$$\begin{array}{c} O \\ A - N \\ O \end{array} \begin{array}{c} O \\ R^{5} \end{array} \begin{array}{c} O \\ R^{5} \end{array} \begin{array}{c} O \\ O \end{array} \begin{array}{c} O \end{array} \begin{array}{c} O \\ O \end{array} \begin{array}{c} O \\ O \end{array} \begin{array}{c} O \end{array} \begin{array}{c} O \\ O \end{array} \begin{array}{c} O \end{array} \begin{array}{c} O \end{array} \begin{array}{c} O \\ O \end{array} \begin{array}{c} O \end{array} \begin{array}{c} O \\ O \end{array} \begin{array}{c} O \end{array} \\ \begin{array}{c} O \end{array} \begin{array}{c} O \end{array} \\ \begin{array}{c}$$

wherein R1, R2, R3, A and

are as defined in Claim 1 and R⁵ is as defined in Claim 2.
9. A compound represented by the general formula (Ie),

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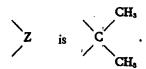
wherein R1, R2, R3, A and

7

are as defined in Claim 1 and R5 is as defined in Claim 2.

10. A compound according to Claim 9, wherein A is a hydrogen atom, or a substituted or unsubstituted alkyl, alkenyl, aryl or aralkyl group; and R² and R³ are individually a hydrogen atom or an alkyl group.

11. A compound according to Claim 5, wherein



12. A compound according to Claim 6, wherein

Z is CC... 10

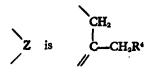
13. A compound according to Claim 7, wherein

14. A compound according to Claim 8, wherein

15. A compound according to Claim 9, wherein

Z is CH_s

16. A compound according to Claim 9, wherein



in which R4 is as defined above.

17. A compound according to Claim 1, wherein R¹ is a hydrogen atom.
18. A compound according to Claim 1, wherein R¹ is selected from ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions and ester-forming groups capable of being easily removed

owing to enzymes in a living body. 19. A compound selected from

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 $6 - [D(-) - \alpha - (4 - n - butyl - 6 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$

65

amino)phenylacetamido]penicillanic acid,

amino) phenylacetamido] penicillanic acid,

	15-003002	
	$6 - [D(-) - \alpha - (4 - benzyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	
	$6 - [D(-) - \alpha - (4 - \beta - \text{hydroxyethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] penicillanic acid,	
5	$6 - [D(-) - \alpha - (4 - acetyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino) -$	5
•	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - carbamoyl - 2 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	
	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (3 - 0x0 - 1 - piperazinocarbonylamino) phenylacetamido] peni-$	
10	cillanic acid, $6 - [D(-) - \alpha - (2,5 - dimethyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	10
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (5 - methyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
15	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (2 - \text{ethoxycarbonylmethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonyl} $	15
	amino) phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (2 - methyl - 3 - oxo - 1 - piperazinocarbonylamino) phenylacet-$	10
	amido penicillanic acid,	
20	$6 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ propionamido] penicillanic acid,	20
	$6 - [D(-) - \alpha - (4 - allyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,$	
	$6 - [D(-) - \alpha - (4 - \alpha - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid,$	-
25	6 - $[D(-) - \alpha - (4 - \beta - methylallyl - 3 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid,$	25
	$6 - \{D(-) - \alpha - [4 - (trans - 2 - butenyl) - 3 - oxo - 1 - piperazinocarbonylamino] phenylacetamido) penicillanic acid,$	
30	$6 - [D(-) - \alpha - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] penicillanic acid.$	30
30	$6 - \{\hat{D}(-) - \alpha - (4 - n - \text{heptyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})\}$	30
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - octyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	
35	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - dodecyl - 3 - oxo - 1 - piperazinocarbonylamino) phenyl-$	35
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{cyclopentyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino}) phenyl-$	
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - phenylaminocarbonyl - 3 - oxo - 1 - piperazinocarbonyl-$	
40	amino)phenylacetamido]penicillanic acid, 6 - $[D(-) - \alpha - (2 - phenyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-$	40
	acetamido] penicillanic acid, and $6 - [D(-) - \alpha - (4 - morpholinomethyl - 3 - oxo - 1 - piperazinocarbonylamino)-$	
45	phenylacetamido] penicillanic acid.	45
43	21. A compound selected from $6 - [D(-) - \alpha - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	43
	acetamido]penicillanic acid, $6 - [D(-) - \alpha - (4 - benzoyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-$	
50	acetamido]penicillanic acid, $6 - [D(-) - \alpha - (4 - methyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-$	50
	acetamido] penicillanic acid, and $6 - [D(-) - \alpha - (4 - benzyl - 2,5 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	
	acetamido]penicillanic àcid. 22. A compound selected from	
55	6 - [D(-) - a - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid,	55
	$6 - [D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ acetamido] penicillanic acid,	
60	$6 - [\hat{D}(-) - \alpha - (4 - n - \text{propyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	66
60	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	60
	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	
	phenylacetamido]penicillanic acid,	

	·	
162	1,508,062	162
	$6 - [D(-) - \alpha - (4 - acetoxyethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	
	phenylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - allyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	•
	acetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenyl-$	5
5	acetamido] penicillanic acid, $6 \cdot [D(-) - \alpha - (4 - \beta - \text{chloroethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$	
•	phenylacetamido I penicillanic, acid.	•
10	6 - [D(-) - α - (6 - methyl - 4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonyl- amino)phenylacetamido]penicillanic acid,	10
10	6 - [D(-) - α - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)- phenylacetamido] penicillanic acid,	
	$6 - [D(-)] - \alpha - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)$	
15	phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-$	15
10	phenylacetamido penicilianic acid, 6 - $[D(-)$ - α - $(4$ - n - heptyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	
	nhanylacetamido l negicillanic, acid.	-
20	6 - $[D(-) - \alpha - (4 - n - \text{octyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] penicillanic acid,	20
	6 - $[D(-)$ - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)- phenylacetamido] penicillanic acid,	
	$6 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phydroxyphenylacetamido] penicillanic acid,$	
. 25	$6 - [D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p$	25 =
	hydroxyphenylacetamido] penicillanic acid, 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4-$	
	cyclonexadienylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - 1,4-$	4
30	cyclohexadienylacetamido] penicillanic acid, 6 - $[D(-)$ - α - $(4$ - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	30
	1 A gyclobevadienylacetamidol penicillanic acid.	
	6 - [D(-) - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1,4- cyclohexadienylacetamido] penicillanic acid,	
35 -	6 - [DL - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocaroonylamino) - 2-	35
	$6 - [DL - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - 2 - \text{thienyl-}$	
	acetamido] penicillanic acid, 6 - [DL - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperadinocarbonylamino) - 2-	40
40	thienylacetamido] penicillanic acid, and 6 - [DL - α - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 2-	40
	thienylacetamido] penicillanic acid. 23. A compound selected from	
	$6 - [D(-)] - \alpha - (2.2 - pentamethylene - 3.5 - dioxo - 1 - piperazinocaroonyl-$	45
45	amino)phenylacetamido]penicillanic acid, $6 - [D(-) - \alpha - (3.5 - \text{diox}o - 1 - \text{piperazinocarbonylamino})$ phenylacetamido]-	. 40
	penicillanic acid, $6 - [D(-) - \alpha - (2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piperazinocarbonyl-$	
50	amino)phenylacetamido] penicillanic acid, $6 - [D(-) - \alpha - (4 - benzyl - 2,2 - pentamethylene - 3,5 - dioxo - 1 - piperazino-$	50
50		
	6 - $[D(-) - \alpha - (4 - \beta_3\beta_3\beta - \text{trichloroethoxycarbonyl} - 2,2 - \text{pentamethylene-}$ 3,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido]penicillanic acid, and	
ee	6 - $[D(-)] - \alpha$ - $(4 - benzyl - 2 - methyl - 2 - phenyl - 3,5 - dioxo - 1 - piper-azinocarbonylamino)phenylacetamido]penicillanic acid.$	55
. 55	24. A compound selected from $7 - [D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenyl-	
	acetemidal 2 methyl - A3 - cephem - 4 - cathoxylic acid.	
60	7 - $[D(-)$ - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocaroonylainino) pitchyl	60 .
w	$7 - [D(-) - \alpha - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocaroonylamino)$	
	7 - (D(-) - a - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarounylainino) piicityl	
65	acetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - n - pentyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-	65
-	· · · · · · · · · · · · · · · · · · ·	

	2,500,002	100
	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - n - hexyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid,	
² 5	7 - $[D(-)$ - α - $(4 - n - \text{heptyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - $(4 - n - \text{octyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ -	5
•	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid,	
10	7 - $[D(-) - \alpha - (4 - n - \text{propyl} - 2, 3 - \text{diox}_0 - 1 - \text{piperazinocarbonylamino})$ - phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{diox}_0 - 1 - \text{piperazinocarbonylamino})$ phenyl-	10
15	acetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)- phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)-	15
20	phenylacetamido] - 3 - acetoxymethyl - Δ^2 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinothiocarbonylamino)- phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D() - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl- acetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem- 4 - carboxylic acid,	20
÷25	7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid, 7 - [D(-) - α - (4 - n - propyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 -	-25
30	cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - $(4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)- phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3- cephem - 4 - carboxylic acid,$	30
35	7 - $[D(-)$ - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2 - (5 - \text{methyl} - 1,3,4 - \text{thiadiazolyl}) - \text{thiomethyl}]$ - Δ^3 - cephem-4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}]$ - Δ^3 - cephem-4 - carboxylic acid,	35
40	7 - $[D(-)$ - α - (4 - ethyl - 6 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}]$ - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - (4,6 - dimethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[5$ - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 -	40
45	cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - phenyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-	45
50	acetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^2 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid,	50
,55	7 - $[D(-)$ - α - $(4$ - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(1$ - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid, 7 - $[D(-)$ - α - $(4$ - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(1$ - methyl - 1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4-	55
60	carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{phenyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})\text{phenyl-acetamido}] - 3 - [2 - (1 - \text{methyl} - 1,3,4 - \text{triazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4-carboxylic acid,$	60
	7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)propionamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p-	

164	1,508,062	164
	hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl]	
	Δ^{0} - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - azidomethyl - Δ^{0} - cephem - 4 - carboxylic acid,	5
5	7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem-4 - carboxylic acid,	*
10	$7 - [D(-)] - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ acetamido] $-3 - [5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}] - \Delta^3 - \text{cephem-}$	10
	7 - [$D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (1,3,4 - triazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic	
15	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^{\alpha} - cephem - 4 - carboxylic acid,$	15
	7 - [D() - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [5 - (1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic	20
20	7 - [D() - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)pnenyl- acetamido] - 3 - [2 - (5 - methyl - 1,3,4 - oxadiazolyl) - thiomethyl] - Δ^3 - cephem-	20
25	7 - $[\dot{\mathbf{D}}(-)] - \alpha$ - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenyl-acetamido] - 3 - [3 - (2,6 - dimethyl - 5 - oxo - 2,5 - dihydro - 1,2,4 - triazinyl)-thiomethyl - Δ^3 - cephem - 4 - carboxylic acid.	25 🗢
20	7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ pnenyl-acetamido] - 3 - $[2 - (4 - \text{methyloxazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4 - carboxylic$	5
30	acid, $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - [2 - (4 - methylthiazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carbonylacetamido$	30
	boxylic acid, 7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenyl-acetamido}] - 3 - [2 - (\text{pyridyl} - 1 - \text{oxide}) - \text{thiomethyl}] - \Delta^3 - \text{cephem} - 4 - \text{carboxylic}$	
35	acid, $7 - [D(-) - \alpha - (4 - methyl - 2, 3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - (2 - thiazolinylthiomethyl) - \Delta^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - \alpha - (4 - methyl - 2, 3 - dioxo - 1 - piperazinocarbonylamino) phenylacetamido] - 3 - [2 - (1 - methylimidazolyl) thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid,$	35
40	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $(2 - \text{pyrimidinylthiomethyl})$ - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] - 3 - $[3 - (6 - \text{methylpyridazinyl})$ - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid	40
45	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ acetamido] - 3 - $[1 - (4 - \text{methyl})]$ piperazino) - thiocarbonylthiomethyl] - Δ^3 - cephem-	45
50	7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (3 - methylisoxazolyl) - carbonylthiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamino$	50
	acetamido] - 3 - ethoxythiocarbonylthiomethyl - Δ^{6} - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - pyridinomethyl - Δ^{3} - cephem - 4 - carboxylic acid betaine, and	
55	7 - $[D(-) - \alpha - (4 - \text{methyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ acetamido] - 3 - pyridinomethyl - Δ^3 - cephem - 4 - carboxylic acid betaine. 25. A compound selected from 7 - $[D(-) - \alpha - (4 - \text{ethoxycarbonyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$	55
60	phenylacetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - $[D(-)]$ - α - (4 - n - hexyl - 3 - oxo - 1 - piperazinocarbonylamino)phenyl-	60
•	acetamido] - 3 - methyl - Δ^3 - cephem - 4 - carboxylic acid, 7 - [D(-) - α - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4- thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-	
65	carboxylic acid, $7 - [D(-) - \alpha - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino)-$	65

	phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^{u} - cephem - 4 - carboxylic acid,	
3	7 - $[D(-) - \alpha - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazoiyl) - thiomethyl] - \Delta^{\alpha} - cephem-$	
5	4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - \text{ethyl} - 2 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	- 5
à	amido] $-3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem - 4-$	
	carboxylic acid, 7 - $[D(-)$ - α - $(4$ - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-	
10	amino) phenylacetamido] - 3 - $[2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic acid,$	10
	7 - $[D(-)$ - α - $(4$ - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - $[2$ - $(5$ - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^3 - cephem - 4-carboxylic acid,	
15	7 - $[D(-)$ - α - (4 - ethyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - Δ^0 - cephem - 4-	15
	carboxylic acid, $7 - [D(-) - \alpha - (3.5 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) \text{phenylacetamido}]$	
20	$3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem - 4 - carboxylic$	20
20	acid, $7 - [D(-) - \alpha - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^a - cephem-$	20,
J	4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - acetyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-$	
້ 25	amido] - 3 - $[5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid.$	25
- .	7 - $[D(-) - \alpha - (4 - methanesulfonyl - 2 - oxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3-$	
20	cephem - 4 - carboxylic acid, 7 - $[D(-) - \alpha - (4 - methyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacet-$	30
30	amido] $-3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,$	
	7 - $[D(-)$ - α - (4 - ethyl - 2 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl- 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-	
35	carboxylic acid, $7 - [D(-) - \alpha - (4 - acetylaminocarbonyl - 2 - oxo - 1 - piperazinocarbonyl-$	35
	amino) phenylacetamido] - 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}] - \Lambda^3 - cephem - 4 - carboxylic acid.$	
40	7 - $[D(-)$ - α - (4 - methyl - 3 - oxo - 1 - piperazinocarbonylamino)phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4-	40
40	carboxylic acid, $7 - [D(-) - \alpha - (4 - \text{ethyl} - 3 - \text{oxo} - 1 - \text{piperazinocarbonylamino})$ phenylacet-	
	amido] $-3 - [5 - (1 - methyl-1,2,3,4 - tetrazolyl) - thiomethyl] - \Delta^3 - cephem - 4-carboxylic acid,$	
45	7 - $[D(-) - \alpha - (3,5 - \text{dioxo} - 1 - \text{piperazinocarbonylamino})$ phenylacetamido] 3 - $[5 - (1 - \text{methyl} - 1,2,3,4 - \text{tetrazolyl}) - \text{thiomethyl}] - \Delta^3 - cephem - 4 - carboxylic$	45
	acid, and $7 - [D(-) - \alpha - (4 - acetyl - 2,5 - dioxo - 1 - piperazinocarbonylamino)phenyl-$	
50	acetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^0 - cephem-4 - carboxylic acid.	50
_	26. A compound selected from pivaloyloxymethyl 6 - $[D(-) - \alpha - (2 - methyl - 3 - oxo - 1 - piperazinocarbonyl-$	
	amino) phenylacetamido] penicillanate, phthalidyl 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	
¹ 55	amino) phenylacetamido) penicillanate, phthalidyl 6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl}$	55
	amino) phenylacetamido] penicillanate, phthalidyl 6 - $[D(-)$ - α - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazinocar-	
	bonylamino) phenylacetamido] penicillanate, phthalidyl $6 - [D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazinocarbonyl-$	60
60	amino) phenylacetamido] penicillanate, methoxymethyl 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-$	- •
	carbonylamino) phenylacetamido) penicillanate, methoxymethyl 6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl} - 2,3 - \text{dioxo} -$	
65	amino) phenylacetamido] penicillanate,	65

•	methoxymethyl 6 - $[D(-) - \alpha - (4 - n - butyl - 2,3 - dioxo - 1 - piperazino-carbonylamino) phenylacetamido) penicillanate,$	
	methoxymethyl 6 - $[D(-) - \alpha - (4 - iso - propyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido] penicillanate,$	£
5	methoxymethyl 6 - $\{D(-) - \alpha - (4 - n - \text{octyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazino-} \}$. 5
•	carbonylamino)phenylacetamido]penicillanate, pivaloyloxymethyl 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-$	7
	carbonylamino)phenylacetamido]penicillanate, pivaloyloxymethyl 6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazino-}$	10
10	carbonylamino)phenylacetamido]penicillanate, pivaloyloxymethyl 6 - $[D(-) - \alpha - (4 - n - \text{octyl} - 2, 3 - \text{diox} - 1 - \text{piperazino-}$	10
	carbonylamino)phenylacetamido)penicillanate, β - piperidinoethyl 6 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-$	
	carbonylamino) phenylacetamido] penicillanate, β - piperidinoethyl 6 - [D(-) - α - (4 - n - octyl - 2,3 - dioxo - 1 - piperazino-	15
15	carbonylamino)phenylacetamido]penicillanate, β - morpholinoethyl 6 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazino-	
	carbonylamino) phenylacetamido l penicillanate.	-
20	β - morpholinoethyl 6 - $[D(-)$ - α - $(4$ - n - octyl - 2,3 - dioxo - 1 - piperazino-carbonylamino)phenylacetamido]penicillanate, and	20
	methoxymethyl 7 - $[D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazino-carbonylamino) phenylacetamido] - 3 - methyl - \Delta^3 - cephem - 4 - carboxylate.$	
	27. A compound according to Claim 1, 5, 6, 7, 8 or 9, wherein R ¹ is a cation capable of forming a non-toxic salt.	
25	28. A non-toxic salt of a compound according to Claim 19, 20, 21, 22, 23, 24 or 25.	25 *
	 6 - [D(-) - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] penicillanic acid or its non-toxic salt. 	9
30	30. 6 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino)-phenylacetamido] penicillanic acid or its non-toxic salt.	30
30	31. $6 - [D(-) - \alpha - (6 - \text{methyl} - 4 - \text{ethyl} - 2,3 - \text{dioxo} - 1 - \text{piperazinocarbonyl-amino})$ phenylacetamido] penicillanic acid or its non-toxic salt.	
	32. 6 - $[D(-) - \alpha - (4 - \text{ethyl} - 2, 3 - \text{dioxo} - 1 - \text{piperazinocarbonylamino}) - p-hydroxyphenylacetamido]penicillanic acid or its non-toxic salt.$	
35	33. $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - [5 - (1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^3 - cephem - 4-$	35
	carboxylic acid or its non-toxic salt. 34. $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -$	
	phenylacetamido] - 3 - $[2 - (5 - methyl - 1,3,4 - thiadiazolyl) - thiomethyl] - \Delta^{-}$	40
40	cephem - 4 - carboxylic acid or its non-toxic salt. 35. $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - 1 - piperazinocarbonylamino - 1 - piperazinocarbonylamino - 1 - piperazinocarbonylamino) - 1 - piperazinocarbonylamino - 1 - piperazinocarb$	
	phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ^3 - cephem - 4 - carboxylic acid or its non-toxic salt.	
45	36. $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - phenylacetamido] - 3 - [2 - (1 - methyl - 1,3,4 - triazolyl) - thiomethyl] - \Delta^3 - cephem-$	45
	4 - carboxylic acid or its non-toxic salt. 37. 7 - $[D(-)$ - α - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -	
	phenylacetamido] - 3 - acetoxymethyl - Δ^3 - cephem - 4 - carboxylic acid or its non-toxic salt.	
50	38. $7 - [D(-) - \alpha - (4 - methyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) - p - hydroxyphenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thio-$	50
	methyl] - Δ^3 - cephem - 4 - carboxylic acid or its non-toxic salt. 39. 7 - [D(-) - α - (4 - ethyl - 2,3 - dioxo - 1 - piperazinocarbonylamino) -	
55	phenylacetamido] - 3 - [5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thiomethyl] - Δ° - cephem - 4 - carboxylic acid or its non-toxic salt.	55 ,
55	40. A process for producing a compound represented by the general formula (I),	

$$A - N = 0$$

$$(R^2 R^3) = 0$$

$$(R^2 R^3) = 0$$

$$(R^3 R^3) = 0$$

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wherein R, A, X, n, m, R₁, R₂, R₃, Y and Z are as herein defined which comprises reacting a compound represented by the general formula (II),

$$R^7$$
-NH -R - CONH Z
COOR,

wherein R' represents a hydrogen atom, a silicon or phosphorous containing group, which is capable of easy removal by treatment with water or an alcohol; R, R¹ and

z

are as defined above, with a reactive derivative in the (thio)carboxyl group of a compound represented by the general formula (III),

$$A - N - C - OH$$

$$(III)$$

wherein A, X, Y, R², R³, n and m are as defined above.
41. A process for producing a compound represented by the general formula (I),

$$A - N_{\frac{5}{3}, \frac{5}{6}}^{\frac{3}{2}} N - C - NH - R - CONH$$

$$(R^2 R^3)_m$$

$$COOR^4$$

wherein A, Y, R, R1, R2, R3, X,

z

n and m are as defined in Claim 40, which comprises reacting a compound represented by the general formula (IV),

wherein R1, R7 and

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are as defined in Claim 40, with a compound represented by the general formula (V), 20

$$A - N = \begin{pmatrix} X \\ N - C \\ R^2 \end{pmatrix}_{M}^{N-C} - NH - R - C - OH$$
 (V)

wherein A, R, R², R³, X, Y, n and m are as defined in Claim 40, or with a reactive derivative in the carboxyl group of the compound of formula (V).

42. A process for producing a compound represented by the general formula (I'),

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$$A = N + C + NH + R = CONH + CONH + CONH + COOR1$$

$$(R^2 R^3)_m$$

$$(R^3 R^4)_m$$

$$(R^3 R^4)_m$$

$$(R^3 R^4)_m$$

$$(R^3 R^4)_m$$

$$(R^3 R^4)_m$$

wherein A, R, R¹, R², R³, X, Y, n and m are as defined in Claim 1 and R^{4a} represents a cyano group, an azido group, a quaternary ammonium group, or a substituted or unsubstituted alkoxy, aryloxy, aralkoxy, acyloxy, carbamoyloxy, guanidino, amino, alkylthio, arylthio, aralkylthio, acylthio, thiocarbamoylthio, alkoxythiocarbonylthio, aryloxythiocarbonylthio, cycloalkyloxythiocarbonylthio, amidinothio, or heterocyclylthio group, which comprises reacting a compound represented by the general formula (VI),

$$A - N + C - NH - R - CONH + CH2B$$

$$(VI)$$

$$(R^2 R^3)_m$$

$$(VI)$$

wherein B represents a substituent capable of being easily replaced by a nucleophilic reagent; and A, R, R¹, R², R³, X, Y, n and m are as defined in Claim 40, with a compound represented by the general formula (VII),

 R^8M (VII)

wherein M represents a hydrogen atom, or an alkali metal or alkaline earth metal atom; and R⁸ represents a cyano group, an azido group or an organic group linked through O, N or S, or with a tertiary amine.

43. A process according to Claim 40, 41 or 42, wherein R is a group represented by the formula,

in which R⁵ is as defined in claim 2.

44. A process according to Claim 40 or 41, wherein

Z is CCH₃

45. A process according to Claim 40 or 41, wherein

in which R* is as defined in Claim 40.

46. A process according to Claim 40 or 41, wherein R is

CH

in which R⁵ is as defined in Claim 43, n is 1, m is 3, and X is an oxygen atom linked to the carbon atom at the 2-position of the piperazine ring.

47. A process according to Claim 40 or 41, wherein R is

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in which R⁵ is as defined in Claim 43, n is 1, m is 3 and X is an oxygen atom linked to the carbon atom at the 3-position of the piperazine ring.

48. A process according to Claim 40 or 41, wherein R is

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in which R⁵ is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 5-positions of the piperazine ring.

49. A process according to Claim 40 or 41, wherein R is

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in which R⁵ is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms linked to the carbon atoms at the 3- and 5-positions of the piperazine ring.

50. A process according to Claim 40 or 41, wherein R is

in which R⁵ is as defined in Claim 43, n is 2, m is 2 and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring.

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51. A process according to Claim 42 or 45, wherein R is

in which R⁵ is as defined in Claim 43; n is 2; m is 2; and the two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring.

52. A process according to Claim 46, wherein

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53. A process according to Claim 47, wherein

54. A process according to Claim 48, wherein

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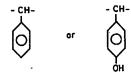
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55. A process according to Claim 49, wherein

56. A process according to Claim 50, wherein

57. A process according to Claim 40, 41 or 42, wherein A is a hydrogen atom, or a substituted or unsubstituted alkyl, alkenyl, aryl or aralkyl group; and R² and R³ are individually a hydrogen atom or an alkyl group.

58. A process according to Claim 40 or 41, wherein R is



n is 2; m is 2 and two X's are oxygen atoms linked to the carbon atoms at the 2- and 3-positions of the piperazine ring, each pair of R² and R³, which may be the same or different, are individually a hydrogen atom or a methyl group, A is a methyl or ethyl group, R¹ is a hydrogen atom or a cation capable of forming a non-toxic salt and

in which R⁴ is an acetoxy, 5 - (2 - methyl - 1,3,4 - thiadiazolyl) - thio, 5 - (1,3,4-thiadiazolyl) - thio, 2 - (1 - methyl - 1,3,4 - triazolyl) - thio, 5 - (1 - methyl - 1,2,3,4-tetrazolyl) - thio or 5 - (1,2,3,4 - tetrazolyl) - thio group.

59. A process according to Claim 42, wherein R is

n is 2, m is 2; two X's are oxygen atoms linked to the carbon atoms at the 2- and 3positions of the piperazine ring; each pair of R² and R³, which may be the same or
different, are individually a hydrogen atom or methyl group; A is a methyl or ethyl
group; and R¹ is a hydrogen atom or a cation capable of forming a non-toxic salt.

60. A process according to Claim 42, wherein R⁴ and R⁸ are the same and selected from, 5 - (2 -methyl - 1,3,4 - thiadiazolyl) - thio, 5 - (1,3,4 - thiadiazolyl) - thio, 5 - (1 - methyl - 1,2,3,4 - tetrazolyl) - thio, and 5 - (1,2,3,4 - tetrazolyl) - thio groups.

61. A process according to Claim 40 or 41, wherein R' is a hydrogen atom.
62. A process according to Claim 40, 41 or 42, wherein R' is a cation capable of forming a salt.
63. A process according to Claim 62, wherein the salt is a non-toxic salt.

64. A process according to Claim 40, 41 or 42 wherein R¹ is selected from the

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group consisting of ester-forming groups capable of being removed by catalytic reduction, chemical reduction or hydrolysis under mild conditions and ester-forming groups capable of being easily removed owing to enzymes in a living body.

65. A process according to Claim 40 or 41, wherein R¹ is a trialkylammonium.

66. A process according to Claim 40, wherein the reactive derivative in the (thio)carboxyl group of a compound of formula (III) is an acid halide.

67. A process according to Claim 41, wherein the reactive derivative in the carboxyl

group of a compound of formula (V) is a mixed acid anhydride.

68. A process according to Claim 40 or 41, wherein the reaction is carried out in

the presence of an acid-binding agent.

69. A process according to Claim 41, wherein the reaction is carried out in the presence of a dehydrating condensing agent.

70. A process according to Claim 40 or 41, wherein at least one of R1 and R7 is a

silicon, or a phosphorus containing group capable of easy removal by treatment with water or an alcohol.

71. A process according to Claim 40 or 41, wherein the reaction is carried out at a temperature of -60° to $+80^{\circ}$ C

72. A process according to Claim 42, wherein B is a halo-substituted or unsubstituted lower alkanoyloxy group.

73. A process according to Claim 42, wherein B is an acetoxy group.

74. A process according to Claim 42, wherein R⁸ is an organic group linked through O or S.

75. A process according to Claim 42, wherein the compound (VII) is selected from

$$\begin{bmatrix}
CH_3 \\
N \\
SH,
N \\
SH,
N \\
N \\
SH$$

$$CH_3$$
 $N = 0$
 $C = SNa$, $C_2H_5O - C - SNa$, and CH_3OH .

76. A process according to Claim 42, wherein the tertiary amine is pyridine.

77. A process according to Claim 42, wherein the reaction is carried out in a polar solvent at a pH of 2 to 10.

78. A process according to Claim 42, wherein the reaction is carried out at a temperature of 0° to 100°C.

79. A process according to Claim 42, wherein B is a hetero aromatic amine N-oxide thio group having a thio group on the carbon atom adjacent to the N-oxide in the molecule, and the reaction is effected in the presence of a cupric compound.

80. A pharmaceutical composition containing as an active ingredient the compound as claimed in Claim 1.

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